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WO 02/30931 A2

(54) Title: AZA- AND POLYAZA-NAPHTHALENYL CARBOXAMIDES USEFUL AS HIV INTEGRASE INHIBITORS

(57) Abstract: Aza- and polyaza-naphthalenyl carboxamide derivatives including certain quinoline carboxamide and naphthyridine carboxamide derivatives are described. These compounds are inhibitors of HIV integrase and inhibitors of HIV replication, and are useful in the prevention or treatment of infection by HIV and the treatment of AIDS, as compounds or pharmaceutically acceptable salts, or as ingredients in pharmaceutical compositions, optionally in combination with other antivirals, immunomodulators, antibiotics or vaccines. Methods of preventing, treating or delaying the onset of AIDS and methods of preventing or treating infection by HIV are also described.

TITLE OF THE INVENTION

AZA- AND POLYAZA-NAPHTHALENYL CARBOXAMIDES USEFUL AS HIV INTEGRASE INHIBITORS

FIELD OF THE INVENTION

The present invention is directed to aza- and polyaza-naphthalenyl carboxamides and pharmaceutically acceptable salts thereof, their synthesis, and their use as inhibitors of the HIV integrase enzyme. The compounds of the present invention include 7-(N-substituted carboxamido)-8-hydroxy- 1,6-naphthyridines, and quinoxalines. The compounds and pharmaceutically acceptable salts thereof of the present invention are useful for preventing or treating infection by HIV and for treating AIDS.

BACKGROUND OF THE INVENTION

A retrovirus designated human immunodeficiency virus (HIV) is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. This virus was previously known as LAV, HTLV-III, or ARV. A common feature of retrovirus replication is the insertion by virally-encoded integrase of proviral DNA into the host cell genome, a required step in HIV replication in human T-lymphoid and monocytoid cells. Integration is believed to be mediated by integrase in three steps: assembly of a stable nucleoprotein complex with viral DNA sequences; cleavage of two nucleotides from the 3' termini of the linear proviral DNA; covalent joining of the recessed 3' OH termini of the proviral DNA at a staggered cut made at the host target site. The fourth step in the process, repair synthesis of the resultant gap, may be accomplished by cellular enzymes.

Nucleotide sequencing of HIV shows the presence of a pol gene in one open reading frame [Ratner, L. et al., Nature, 313, 277(1985)]. Amino acid sequence homology provides evidence that the pol sequence encodes reverse transcriptase, integrase and an HIV protease [Toh, H. et al., EMBO J. 4, 1267 (1985); Power, M.D. et al., Science, 231, 1567 (1986); Pearl, L.H. et al., Nature, 329, 351 (1987)]. All three enzymes have been shown to be essential for the replication of HIV.

It is known that some antiviral compounds which act as inhibitors of HIV replication are effective agents in the treatment of AIDS and similar diseases, including reverse transcriptase inhibitors such as azidothymidine (AZT) and efavirenz and protease inhbitors such as indinavir and nelfinavir. The compounds of this invention are inhibitors of HIV integrase and inhibitors of HIV replication. The inhibition of integrase in vitro and HIV replication in cells is a direct result of inhibiting the strand transfer reaction catalyzed by the recombinant integrase in vitro in HIV infected cells. The particular advantage of the present invention is highly specific inhibition of HIV integrase and HIV replication.

The following references are of interest as background:

Chemical Abstracts No. 33-2525 discloses the preparation of 5-chloro-8-hydroxy-1,6-naphthyridine-7-carboxylic acid amide from the corresponding methyl ester.

Derwent Abstract No. 97-048296 is an abstract of Japanse Published Application No. 08301849. The abstract discloses certain heterocyclic carboxamide derivatives. The derivatives are said to be useful as tachykinin receptor inhibitors. *N*-(3,5-bis(trifluoromethyl)benzyl-1,2-dihydro-*N*,2-dimethyl-1-oxo-4-pyrrolidino-3-isoquinoline carboxamide is specifically disclosed.

WO 98/13350 discloses certain quinoline derivatives which inhibit vascular endothelial growth factor. The reference also discloses certain 1,8-naphthryidine derivatives; i.e., Examples 53 and 54 respectively describe preparations of 2-acetamido-5-(2-fluoro-5-hydroxy-4-methylanilino)-1,8-naphthyridine and 2-amino-5-(2-fluoro-5-hydroxy-4-methylanilino)-1,8-naphthyridine.

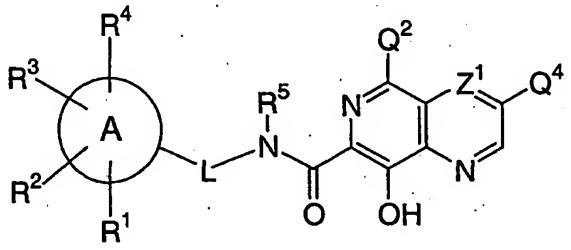
WO 99/32450 discloses 4-hydroxyquinoline-2-carboxamide derivatives which are proposed for use in treating herpes virus infections.

WO 98/11073 discloses 8-hydroxyquinoline-7carboxamides which are proposed for use in treating herpes virus infections.

SUMMARY OF THE INVENTION

The present invention is directed to novel aza- and polyaza-naphthalenyl carboxamides. These compounds are useful in the inhibition of HIV integrase, the prevention of infection by HIV, the treatment of infection by HIV and in the prevention, treatment, and delay in the onset of AIDS and/or ARC, either as compounds or their pharmaceutically acceptable salts or hydrates (when appropriate),

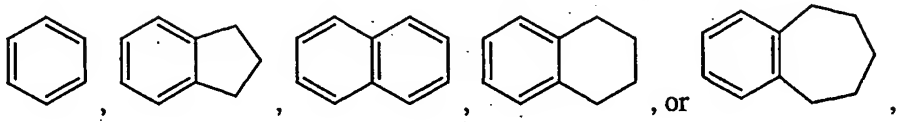
or as pharmaceutical composition ingredients, whether or not in combination with other HIV/AIDS antivirals, anti-infectives, immunomodulators, antibiotics or vaccines. More particularly, the present invention includes a compound of Formula (I):



(I),

wherein

A is



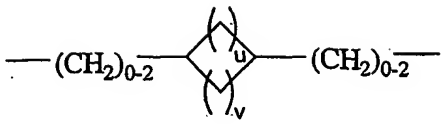
L is

(i) a single bond;

(ii) $-(CH_2)_{1-3}-$, which is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, -OH, $-C_{1-4}$ alkyl, $-O-C_{1-4}$ alkyl, $-CO_2CH_3$, $-CO_2CH_2$-phenyl, phenyl, benzyl, $-(CH_2)_{1-2}OH$, -CH(OH)-phenyl, and $-CH(NH_2)$-phenyl;

(iii) $-(CH_2)_{0-1}-CH=CH-(CH_2)-$, which is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, -OH, $-C_{1-4}$ alkyl, and $-O-C_{1-4}$ alkyl;

(iv)



, wherein u and v are each integers having a value of from 0 to 4, provided that the sum of u + v is 1, 2, 3 or 4; or

(v) a heteroatom-containing chain which is -N(R^a)-(CH_2)1-2-, -CH_2-OC(=O)-CH_2-, or -CH_2-C(=O)O-CH_2-;

Z^1 is N or C-Q^3;

Q^2 and Q^3 are as defined in (i) or (ii) as follows:

(i) Q^2 is

(1) -H,
(2) -C_{1-4} alkyl,
(3) -C_{1-4} fluoroalkyl,
(4) -O-C_{1-4} alkyl,
(5) -O-C_{1-4} fluoroalkyl,
(6) halo,
(7) -CN,
(8) -C_{1-4} alkyl-OR^a,
(9) -$(CH_2)_{0-2}C(=O)R^a$,
(10) -$(CH_2)_{0-2}CO_2R^a$,
(11) -$(CH_2)_{0-2}SR^a$,
(12) -$N(R^a)_2$,
(13) -C_{1-4} alkyl -$N(R^a)_2$,
(14) -$(CH_2)_{0-2}C(=O)N(R^a)_2$,
(15) -G-C_{1-6} alkyl-$C(=O)N(R^a)_2$, wherein G is O, S, $N(R^a)$, or $N(SO_2R^a)$,
(16) -$N(R^a)$-$C(R^a)$=O,
(17) -$(CH_2)_{1-3}$-$N(R^a)$-$C(R^a)$=O,
(18) -C(=O)-$N(R^a)$-$(CH_2)_{1-3}$-$[C(=O)]_{0-1}$-$N(R^a)_2$,
(19) -C(=O)-$N(R^a)$-C_{1-4} alkyl substituted with 1 or 2 -OR^a,
(20) -SO_2R^a,
(21) -$N(R^a)SO_2R^a$,

(22) -C_{2-4} alkenyl,

(23) -C_{2-4} alkenyl-C(=O)-$N(R^a)_2$,

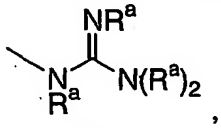
(24) -C_{2-3} alkynyl,

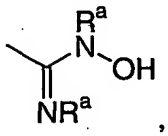
(25) $—C\equiv C—CH_2N(R^a)_2$,

(26) $—C\equiv C—CH_2OR^a$,

(27) $—C\equiv C—CH_2SR^a$,

(28) $—C\equiv C—CH_2SO_2R^a$,

(29)  ,

(30)  ,

(31) -$N(R^a)$-C_{1-4} alkyl-SR^a,

(32) -$N(R^a)$-C_{1-4} alkyl-OR^a,

(33) -$N(R^a)$-C_{1-4} alkyl-$N(R^a)_2$,

(34) -$N(R^a)$-C_{1-4} alkyl-$N(R^a)$-$C(R^a)$=O,

(35) -$N(R^a)$-C_{0-4} alkyl-$[C(=O)]_{1-2}N(R^a)_2$,

(36) -$N(R^a)$-C_{1-4} alkyl-CO_2R^a,

(37) -$N(R^a)C(=O)N(R^a)$-C_{1-4} alkyl-$C(=O)N(R^a)_2$,

(38) -$N(R^a)C(=O)$-C_{1-4} alkyl-$N(R^a)_2$,

(39) -$N(R^a)$-SO_2-$N(R^a)_2$,

(40) -R^k,

(41) -C_{1-4} alkyl substituted with R^k,

(42) -C_{1-4} fluoroalkyl substituted with R^k,

(43) -C_{2-5} alkenyl-R^k,

(44) -C_{2-5} alkynyl-R^k,

(45) -O-R^k,

(46) -O-C_{1-4} alkyl-R^k,

(47) -$S(O)_n$-R^k,

(48) -$S(O)_n$-C_{1-4} alkyl-R^k,

(49) -O-C_{1-4} alkyl-OR^k,

(50) -O-C_{1-4} alkyl-O-C_{1-4} alkyl-R^k,

(51) -O-C_{1-4} alkyl-$S(O)_nR^k$,

(52) -N(R^c)-R^k,
(53) -N(R^c)-C_{1-4} alkyl substituted with one or two R^k groups,
(54) -N(R^c)-C_{1-4} alkyl-OR^k,
(55) -C(=O)-R^k,
(56) -C(=O)N(R^a)-R^k,
(57) -N(R^a)C(=O)-R^k,
(58) -C(=O)N(R^a)-C_{1-4} alkyl-R^k, or
(59) -N(R^a)-C_{0-4} alkyl-S(O)$_n$$R^k$;

Q^3 is
(1) -H,
(2) -C_{1-4} alkyl,
(3) -C_{1-4} fluoroalkyl,
(4) -O-C_{1-4} alkyl,
(5) -O-C_{1-4} fluoroalkyl,
(6) halo selected from -F, -Cl, and -Br,
(7) -CN,
(8) -C_{1-4} alkyl-OR^a, or
(9) -C_{1-4} alkyl substituted with R^k; or

(ii) alternatively, Q^2 and Q^3 together with the carbon atoms to which they are attached and the fused ring carbon atom attached therebetween form a 5- or 6-membered monocyclic heterocycle, wherein the heterocycle contains 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur, and wherein the heterocycle is optionally substituted with from 1 to 3 substituents independently selected from
(1) -C_{1-4} alkyl,
(3) -C_{1-4} fluoroalkyl,
(4) -O-C_{1-4} alkyl,
(5) -O-C_{1-4} fluoroalkyl,
(6) halo,
(7) -CN,
(8) -C_{1-4} alkyl-OR^a,
(9) -C_{1-4} alkyl-S(O)$_n$$R^a$,
(10) -C_{1-4} alkyl-N(R^a)$_2$,

(11) -C_{1-4} alkyl-C(=O)-$N(R^a)_2$,
(12) -C_{1-4} alkyl-CO_2R^a,
(13) oxo,
(14) -R^k, and
(15) -C_{1-4} alkyl substituted with R^k;

Q^4 is:

(1) -H,
(2) -C_{1-4} alkyl,
(3) -C_{1-4} fluoroalkyl,
(4) -O-C_{1-4} alkyl,
(5) -O-C_{1-4} fluoroalkyl,
(6) halo selected from -F, -Cl, and -Br,
(7) -CN,
(8) -C_{1-6} alkyl-OR^a,
(9) -$N(R^a)_2$, or
(10) -C_{1-6} alkyl -$N(R^a)_2$;

each of R^1 and R^2 is independently:

(1) -H,
(2) -C_{1-4} alkyl,
(3) -C_{1-4} fluoroalkyl,
(4) -O-C_{1-4} alkyl,
(5) -O-C_{1-4} fluoroalkyl,
(6) -OH,
(7) halo,
(8) -CN,
(9) -C_{1-4} alkyl-OR^a,
(10) -$(CH_2)_{0-2}C(=O)R^a$,
(11) -$(CH_2)_{0-2}CO_2R^a$,
(12) -$(CH_2)_{0-2}SR^a$,
(13) -$N(R^a)_2$,
(14) -C_{1-4} alkyl $N(R^a)_2$,
(15) -$(CH_2)_{0-2}C(=O)N(R^a)_2$,

(16) -C_{1-4} alkyl-$N(R^a)$-$C(R^a)$=O,
(17) -SO_2R^a,
(18) -$N(R^a)SO_2R^a$,
(19) -O-C_{1-4} alkyl-OR^a,
(20) -O-C_{1-4} alkyl-SR^a,
(21) -O-C_{1-4} alkyl-NH-CO_2R^a,
(22) -O-C_{2-4} alkyl-$N(R^a)_2$,
(23) -$N(R^a)$-C_{1-4} alkyl-SR^a,
(24) -$N(R^a)$-C_{1-4} alkyl-OR^a,
(25) -$N(R^a)$-C_{1-4} alkyl-$N(R^a)_2$,
(26) -$N(R^a)$-C_{1-4} alkyl-$N(R^a)$-$C(R^a)$=O,
(27) -R^k,
(28) -C_{1-4} alkyl substituted with 1 or 2 R^k groups,
(29) -C_{1-4} fluoroalkyl substituted with 1 or 2 R^k groups,
(30) -O-R^k,
(31) -O-C_{1-4} alkyl-R^k,
(32) -$S(O)_n$-R^k,
(33) -$S(O)_n$-C_{1-4} alkyl-R^k,
(34) -O-C_{1-4} alkyl-OR^k,
(35) -O-C_{1-4} alkyl-O-C_{1-4} alkyl-R^k,
(36) -O-C_{1-4} alkyl-$S(O)_nR^k$, or
(37) -C_{0-4} alkyl-$N(R^b)(R^k)$;

each of R^3 and R^4 is independently
(1) -H,
(2) halo,
(3) -CN,
(4) -OH,
(5) C_{1-4} alkyl,
(6) C_{1-4} fluoroalkyl,
(7) -O-C_{1-4} alkyl,
(8) -O-C_{1-4} fluoroalkyl,
(9) -C_{1-4} alkyl-OR^a,
(10) -O-C_{1-4} alkyl-OR^a,

(11) -O-C_{1-4} alkyl-SR^a,
(12) -O-C_{1-4} alkyl-NH-CO_2R^a, or
(13) -O-C_{2-4} alkyl-$N(R^a)_2$;

R^5 is
(1) -H,
(2) -C_{1-4} alkyl, optionally substituted with 1 or 2 substituents independently selected from halogen, -O-C_{1-4} alkyl, -O-C_{1-4} fluoroalkyl, $-N(R^a)_2$, and $-CO_2R^a$;
(3) phenyl optionally substituted with from 1 to 3 substituents independently selected from halogen, C_{1-4} alkyl, C_{1-4} fluoroalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} fluoroalkyl, -S-C_{1-4} alkyl, -CN, and -OH, or
(4) -C_{1-4} alkyl substituted with phenyl;

each R^a is independently -H or -C_{1-4} alkyl;

each R^b is independently:
(1) -H,
(2) -C_{1-4} alkyl,
(3) -C_{1-4} fluoroalkyl,
(4) $-R^k$,
(5) -C_{1-4} alkyl-R^k,
(6) $-S(O)_n-R^k$, or
(7) $-C(=O)-R^k$;

each R^c is independently
(1) -H,
(2) -C_{1-4} alkyl,
(3) -C_{1-4} alkyl substituted with $-N(R^a)_2$, or
(4) -C_{1-4} alkyl-phenyl, wherein the phenyl is optionally substituted with 1 to 3 substituents independently selected from halogen, C_{1-4} alkyl, C_{1-4} fluoroalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} fluoroalkyl, -S-C_{1-4} alkyl, -CN, and -OH;

each R^k is independently:

(1) aryl selected from phenyl and naphthyl, wherein aryl is unsubstituted or substituted with from 1 to 5 substituents independently selected from:

(a) halogen,
(b) C_{1-6} alkyl,
(c) C_{1-6} fluoroalkyl,
(d) -O-C_{1-6} alkyl,
(e) -O-C_{1-6} fluoroalkyl,
(f) phenyl,
(g) -S-C_{1-6} alkyl,
(h) -CN,
(i) -OH,
(j) phenyloxy, unsubstituted or substituted with from 1 to 3 substituents independently selected from:
  (i) halogen,
  (ii) C_{1-6} alkyl,
  (iii) C_{1-6} fluoroalkyl, and
  (iv) -OH,
(k) $-N(R^a)_2$,
(l) -C_{1-6} alkyl-$N(R^a)_2$,
(m) $-R^t$,
(p) $-(CH_2)_{0-3}C(=O)N(R^a)_2$, and
(q) $-(CH_2)_{0-3}C(=O)R^a$;

(2) -C_{3-7} cycloalkyl, unsubstituted or substituted with from 1 to 3 substituents independently selected from:

(a) halogen,
(b) C_{1-6} alkyl,
(c) -O-C_{1-6} alkyl,
(d) C_{1-6} fluoroalkyl,
(e) -O-C_{1-6} fluoroalkyl,
(f) -CN,
(h) phenyl, and
(j) -OH;

(3) -C_{3-7} cycloalkyl fused with a phenyl ring, unsubstituted or substituted with from 1 to 5 substituents independently selected from:

(a) halogen,
(b) C_{1-6} alkyl,
(c) -O-C_{1-6} alkyl,
(d) C_{1-6} fluoroalkyl,
(e) -O-C_{1-6} fluoroalkyl,
(f) -CN, and
(g) -OH;

(4) a 5- or 6- membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur, wherein the heteroaromatic ring is unsubstituted or substituted on nitrogen or carbon with from 1 to 5 substituents independently selected from:

(a) halogen,
(b) C_{1-6} alkyl,
(c) C_{1-6} fluoroalkyl,
(d) -O-C_{1-6} alkyl,
(e) -O-C_{1-6} fluoroalkyl,
(f) phenyl,
(g) -S-C_{1-6} alkyl,
(h) -CN,
(i) -OH,
(j) phenyloxy, unsubstituted or substituted with from 1 to 3 substituents independently selected from:
  (i) halogen,
  (ii) C_{1-6} alkyl,
  (iii) C_{1-6} fluoroalkyl, and
  (iv) -OH,
(k) -$N(R^a)_2$,
(l) -C_{1-6} alkyl-$N(R^a)_2$,
(m) -Rt,
(n) oxo,
(o) -$(CH_2)_{0-3}C(=O)N(R^a)_2$, and
(p) -$(CH_2)_{0-3}C(=O)R^a$;

(5) a 5- or 6- or 7- membered saturated heterocyclic ring containing from 1 to 3 heteroatoms independently selected from oxygen, nitrogen and sulfur, wherein the heterocyclic ring is unsubstituted or substituted with from 1 to 4 substituents independently selected from:

(a) halogen,
(b) C_{1-6} alkyl,
(c) -O-C_{1-6} alkyl,
(d) C_{1-6} fluoroalkyl,
(e) -O-C_{1-6} fluoroalkyl,
(f) -CN,
(g) oxo,
(h) phenyl
(i) benzyl,
(j) phenylethyl,
(k) -OH,
(l) $-(CH_2)_{0-3}C(=O)N(R^a)_2$,
(m) $-(CH_2)_{0-3}C(=O)R^a$,
(n) $-N(R^a)-C(=O)R^a$,
(o) $-N(R^a)-CO_2R^a$,
(p) $-(CH_2)_{1-3}N(R^a)-C(=O)R^a$,
(q) $-N(R^a)_2$,
(r) $-(CH_2)_{1-3}N(R^a)_2$,
(s) $-(CH_2)_{1-3}-OR^a$,
(t) $-(CH_2)_{0-3}CO_2R^a$,
(u) $-(CH_2)_{0-3}-O-(CH_2)_{1-3}-OR^a$,
(v) $-SO_2R^a$,
(w) $-SO_2N(R^a)_2$,
(x) $-(CH_2)_{0-3}C(=O)O(CH_2)_{1-2}CH=CH_2$,
(y) $-R^t$,
(z) $-(CH_2)_{0-3}C(=O)R^t$,
(aa) $-N(R^a)R^t$, and
(bb) $-(CH_2)_{1-3}R^t$; or

(6) an 8- to 10- membered heterobicyclic ring containing from 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur, wherein the

heterobicyclic ring is saturated or unsaturated, and is unsubstituted or substituted with from 1 to 5 substituents independently selected from:

(a) halogen,
(b) C_{1-6} alkyl,
(c) -O-C_{1-6} alkyl,
(d) C_{1-6} fluoroalkyl,
(e) -O-C_{1-6} fluoroalkyl,
(f) -CN,
(g) =O, and
(h) -OH;

R^t is naphthyl or a 5- or 6-membered heteromonocylic ring containing from 1 to 4 nitrogen atoms, wherein the heteromonocyclic ring is saturated or unsaturated, and wherein the naphthyl or the heteromonocyclic ring is unsubstituted or substituted with from 1 to 4 substituents independently selected from halogen, oxo, C_{1-4} alkyl, and -O-C_{1-4} alkyl; and

n is an integer equal to 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

In an aspect of the fifth embodiment, the compound of Formula (I) is as just defined above, except that part (i) of the definition of Q^2 does not include (59) -N(R^a)-C_{0-4} alkyl-S(O)$_n$$R^k$.

The present invention also includes pharmaceutical compositions containing a compound of the present invention and methods of preparing such pharmaceutical compositions. The present invention further includes methods of treating AIDS, methods of delaying the onset of AIDS, methods of preventing AIDS, methods of preventing infection by HIV, and methods of treating infection by HIV.

Other embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing description, examples and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

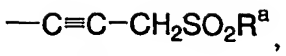
The present invention includes the aza- and polyaza-naphthalenyl carboxamides of Formula (I) above. These compounds and pharmaceutically acceptable salts thereof are HIV integrase inhibitors.

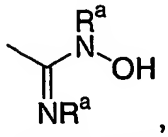
A second embodiment of the invention is a compound of Formula (I), wherein

Z^1 is CH;

Q^2 is

(1) -H,
(2) -C_{1-4} alkyl,
(3) -$(CH_2)_{0-2}CF_3$,
(4) -O-C_{1-4} alkyl,
(5) -O-$(CH_2)_{0-2}CF_3$,
(6) halo selected from -F, -Cl and -Br,
(7) -CN,
(8) -$(CH_2)_{1-3}OR^a$,
(9) -$(CH_2)_{0-2}C(=O)R^a$,
(10) -$(CH_2)_{0-2}CO_2R^a$,
(11) -$(CH_2)_{0-2}SR^a$,
(12) -$N(R^a)_2$,
(13) -$(CH_2)_{1-3}N(R^a)_2$,
(14) -$(CH_2)_{0-2}C(=O)N(R^a)_2$,
(15) -G-$(CH_2)_{1-2}$-$C(=O)N(R^a)_2$, wherein G is O, S, $N(R^a)$, or $N(SO_2R^a)$,
(16) -$N(R^a)$-$C(R^a)$=O,
(17) -$(CH_2)_{1-2}$-$N(R^a)$-$C(R^a)$=O,
(18) -C(=O)-$N(R^a)$-$(CH_2)_{1-3}$-$[C(=O)]_{0-1}$-$N(R^a)_2$,
(19) -C(=O)-$N(R^a)$-$(CH_2)_{1-2}$H substituted with 1 or 2 -OR^a,
(20) -SO_2R^a,
(21) -$N(R^a)SO_2R^a$,
(22) -CH=CH-$(CH_2)_{0-1}$-C(=O)-$N(R^a)_2$,
(23) $—C{\equiv}C—CH_2OR^a$,
(24) $—C{\equiv}C—CH_2SR^a$,

(25)  ,

(26)  ,

(27) -N(Ra)-(CH2)1-4SRa,

(28) -N(Ra)-(CH2)1-4ORa,

(29) -N(Ra)-(CH2)1-4-N(Ra)2,

(30) -N(Ra)-(CH2)1-4N(Ra)-C(Ra)=O,

(31) -N(Ra)-(CH2)0-2-[C(=O)]1-2N(Ra)2,

(32) -N(Ra)-(CH2)1-4-CO2Ra,

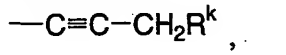
(33) -N(Ra)C(=O)N(Ra)-(CH2)1-4-C(=O)N(Ra)2,

(34) -N(Ra)C(=O)-(CH2)1-4-N(Ra)2,

(35) -N(Ra)-SO2-N(Ra)2,

(36) -Rk,

(37) -(CH2)1-4Rk,

(38)  ,

(39) -O-Rk,

(40) -S(O)n-Rk,

(41) -N(Rc)-Rk,

(42) -N(Rc)-(CH2)1-4H substituted with one or two Rk groups,

(43) -N(Rc)-(CH2)1-4ORk,

(44) -C(=O)-Rk,

(45) -C(=O)N(Ra)-Rk,

(46) -N(Ra)C(=O)-Rk, or

(47) -C(=O)N(Ra)-(CH2)1-4Rk; and

(48) -N(Ra)-S(O)nRk;

Q4 is -H;

each of R1 and R2 is independently:

(1) -H,

(2) -C1-4 alkyl,

(3) -(CH2)0-2CF3,

(4) -O-C1-4 alkyl,

(5) $-O-(CH_2)_{0-2}CF_3$,
(6) -OH,
(7) halo selected from -F, -Cl and -Br,
(8) -CN,
(9) $-(CH_2)_{1-3}OR^a$,
(10) $-(CH_2)_{0-2}C(=O)R^a$,
(11) $-(CH_2)_{0-2}CO_2R^a$,
(12) $-(CH_2)_{0-2}SR^a$,
(13) $-N(R^a)_2$,
(14) $-(CH_2)_{1-3}N(R^a)_2$,
(15) $-(CH_2)_{0-2}C(=O)N(R^a)_2$,
(16) $-C_{1-4}$ alkyl-$N(R^a)-C(R^a)=O$,
(17) $-SO_2R^a$,
(18) $-N(R^a)SO_2R^a$,
(19) $-O-(CH_2)_{1-4}OR^a$,
(20) $-O-(CH_2)_{1-4}SR^a$,
(21) $-O-(CH_2)_{1-4}NH-CO_2R^a$,
(22) $-O-(CH_2)_{2-4}N(R^a)_2$,
(23) $-N(R^a)-(CH_2)_{1-4}SR^a$,
(24) $-N(R^a)-(CH_2)_{1-4}OR^a$,
(25) $-N(R^a)-(CH_2)_{1-4}N(R^a)_2$,
(26) $-N(R^a)-(CH_2)_{1-4}N(R^a)-C(R^a)=O$,
(27) $-R^k$,
(28) $-(CH_2)_{1-4}$H substituted with 1 or 2 R^k groups,
(29) $-O-R^k$,
(30) $-O-(CH_2)_{1-4}R^k$,
(31) $-S(O)_n-R^k$,
(32) $-S(O)_n-(CH_2)_{1-4}R^k$,
(33) $-O-(CH_2)_{1-4}OR^k$,
(34) $-O-(CH_2)_{1-4}-O-(CH_2)_{1-4}R^k$,
(35) $-O-(CH_2)_{1-4}SR^k$, or
(36) $-(CH_2)_{0-4}N(R^b)(R^k)$;

each of R^3 and R^4 is independently

(1) -H,
(2) halo selected from -F, -Cl and -Br,
(3) -CN,
(4) -OH,
(5) C_{1-4} alkyl,
(6) $-(CH_2)_{0-2}CF_3$,
(7) $-O-C_{1-4}$ alkyl, or
(8) $-O(CH_2)_{0-2}CF_3$; and

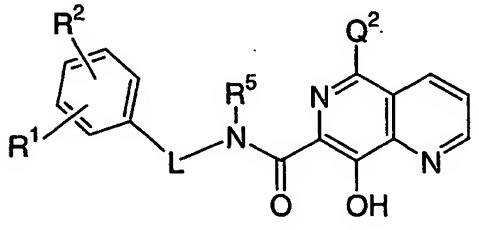
R^5 is

(1) -H,
(2) $-C_{1-4}$ alkyl,
(3) $-(CH_2)_{1-4}N(R^a)_2$,
(4) $-(CH_2)_{1-4}CO_2R^a$,
(5) phenyl optionally substituted with from 1 to 3 substituents independently selected from halogen, C_{1-4} alkyl, $-(CH_2)_{0-2}CF_3$, $-O-C_{1-4}$ alkyl, $-O(CH_2)_{0-2}CF_3$, $-S-C_{1-4}$ alkyl, -CN, and -OH, or
(6) $-(CH_2)_{1-4}$-phenyl;

and all other variables are as originally defined;

or a pharmaceutically acceptable salt thereof.

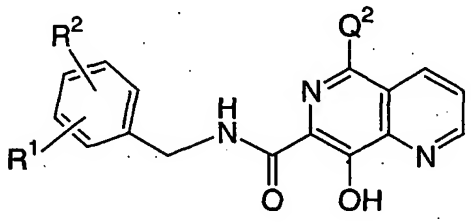
A third embodiment of the present invention is compounds of Formula (II):



(II);

wherein each of the variables is as originally defined or as defined in the second embodiment; or a pharmaceutically acceptable salt thereof.

A first class of the present invention is compounds of Formula (III):



(III);

wherein each of the variables is as originally defined or as defined in the preceding embodiments; or a pharmaceutically acceptable salt thereof.

Exemplary compounds of the invention include compounds selected from the group consisting of

N-(3,5-dichlorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-(2,5-dichlorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-[(1R,S)-2,3-dihydro-1H-inden-1-yl]-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-[2-(3-chlorophenyl)ethyl]-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-[2-(2-chlorophenyl)ethyl]-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-[2-(1,1'-biphenyl-4-yl)ethyl]-8-hydroxy-1,6-naphthyridine-7-carboxamide;

8-hydroxy-N-[2-(4-phenoxyphenyl)ethyl]-1,6-naphthyridine-7-carboxamide;

8-hydroxy-N-(3-phenylpropyl)-1,6-naphthyridine-7-carboxamide;

N-(1,1'-biphenyl-2-ylmethyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-(1,1'-biphenyl-3-ylmethyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

8-hydroxy-N-phenyl-1,6-naphthyridine-7-carboxamide;

8 N-(2-chlorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-benzyl-8-hydroxy-N-methyl-1,6-naphthyridine-7-carboxamide;

8-hydroxy-N-(1-methyl-1-phenylethyl)-1,6-naphthyridine-7-carboxamide;

8-hydroxy-N-(2-phenylethyl)-1,6-naphthyridine-7-carboxamide;

8-hydroxy-N-(1-naphthylmethyl)-1,6-naphthyridine-7-carboxamide;

N-benzyl-8-hydroxy-N-phenyl-1,6-naphthyridine-7-carboxamide;

N-(3-chlorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-(4-chlorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

Methyl (2S)-{[(8-hydroxy-1,6-naphthyridin-7-yl)carbonyl]amino} (phenyl)ethanoate;

Ethyl N-benzyl-N-[(8-hydroxy-1,6-naphthyridin-7-yl)carbonyl]glycinate;

N-benzyl-8-hydroxy-N-(2-phenylethyl)-1,6-naphthyridine-7-carboxamide;

N-(1,2-diphenylethyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-(2,3-dihydro-1H-inden-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-benzyl-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-(2-anilinoethyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-(2,2-diphenylethyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-(3,3-diphenylpropyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-(2-chloro-6-phenoxybenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

Methyl (2R)-{[(8-hydroxy-1,6-naphthyridin-7-yl)carbonyl]amino} (phenyl)ethanoate;

8-hydroxy-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-1,6-naphthyridine-7-carboxamide;

N-(2,3-dihydro-1H-inden-1-ylmethyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

8-hydroxy-N-(6,7,8,9-tetrahydro-5H-benzo[a][7]annulen-6-ylmethyl)-1,6-naphthyridine-7-carboxamide;

8-hydroxy-N-[2-(1-naphthylamino)ethyl]-1,6-naphthyridine-7-carboxamide;

N-(2,3-dihydro-1H-inden-2-ylmethyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

8-hydroxy-N-[(1R)-1-phenylethyl]-1,6-naphthyridine-7-carboxamide;

8-hydroxy-N-[(1S)-1-phenylethyl]-1,6-naphthyridine-7-carboxamide;

8-hydroxy-N-(3-hydroxy-1-phenylpropyl)-1,6-naphthyridine-7-carboxamide;

N-[2-(4-chlorophenyl)ethyl]-8-hydroxy-1,6-naphthyridine-7-carboxamide;

8-hydroxy-N-[(1R)-2-hydroxy-1-phenylethyl]-1,6-naphthyridine-7-carboxamide;

N-[(1S)-1-benzyl-2-hydroxyethyl]-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-[(1R)-1-benzyl-2-hydroxyethyl]-8-hydroxy-1,6-naphthyridine-7-carboxamide;

8-hydroxy-N-(2-hydroxy-2-phenylethyl)-1,6-naphthyridine-7-carboxamide;

5-chloro-N-(3,5-dichlorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-piperidin-1-yl-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-phenyl-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-(1H-imidazol-1-yl)-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-morpholin-4-yl-1,6-naphthyridine-7-carboxamide;

(±)-8-hydroxy-N-[(*cis*)-3-phenyl-2,3-dihydro-1H-inden-1-yl]-1,6-naphthyridine-7-carboxamide

5-bromo-N-(3,5-dichlorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-(benzyl)-8-hydroxy-5-phenyl-1,6-naphthyridine-7-carboxamide;

N-(2,3-dihydro-1H-inden-1-yl)-8-hydroxy-5-phenyl-1,6-naphthyridine-7-carboxamide;

8-hydroxy-N-(1-naphthylmethyl)-5-phenyl-1,6-naphthyridine-7-carboxamide;

N-(2,5-dichlorobenzyl)-8-hydroxy-5-phenyl-1,6-naphthyridine-7-carboxamide;

N-(3-chlorobenzyl)-8-hydroxy-5-phenyl-1,6-naphthyridine-7-carboxamide;

N-[(1S)-2,3-dihydro-1H-inden-1-yl]-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-phenoxy-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-(4-methylpiperazin-1-yl)-1,6-naphthyridine-7-carboxamide;

5-(4-benzylpiperazin-1-yl)-N-(3,5-dichlorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-5-{4-[2-(formylamino)ethyl]piperazin-1-yl}-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-(4-pyridin-2-ylpiperazin-1-yl)-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-(4-pyrrolidin-1-ylpiperidin-1-yl)-1,6-naphthyridine-7-carboxamide;

5-anilino-N-(3,5-dichlorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-5-{[3-(formylamino)propyl]amino}-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-5-{[2-(dimethylamino)ethyl]amino}-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-[(2-morpholin-4-ylethyl)amino]-1,6-naphthyridine-7-carboxamide;

5-[(1-benzylpiperidin-4-yl)amino]-N-(3,5-dichlorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-5-[[2-(dimethylamino)ethyl](methyl)amino]-8-hydroxy-1,6-naphthyridine-7-carboxamide;

8-Hydroxy-5-phenylsulfanyl-[1,6]naphthyridine-7-carboxylic acid 3,5-dichlorobenzylamide;

5-benzenesulfonyl-8-hydroxy-[1,6]naphthyridine-7-carboxylic acid 3,5-dichlorobenzylamide;

tert-butyl 1-(7-{[(3,5-dichlorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)pyrrolidin-3-ylcarbamate;

5-(3-aminopyrrolidin-1-yl)-N-(3,5-dichlorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide trifluoroacetate;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-(4*H*-1,2,4-triazol-4-yl)-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-(1*H*-1,2,4-triazol-1-yl)-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-(3-hydroxypyrrolidin-1-yl)-1,6-naphthyridine-7-carboxamide;

5-[3-(acetylamino)pyrrolidin-1-yl]-*N*-(3,5-dichlorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-5-(4-formylpiperazin-1-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

1-(7-{[(3,5-dichlorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)piperazine;

8-Hydroxy-5-(3-hydroxy-prop-1-ynyl)-[1,6]naphthyridine-7-carboxylic acid 3,5-dichloro-benzylamide;

1-(7-{[(3,5-dichlorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)-4-(2-oxo-2-pyrrolidin-1-ylethyl)piperazine;

8-Hydroxy-5-(3-piperidin-1-yl-prop-1-ynyl)-[1,6]naphthyridine-7-carboxylic acid 3,5-dichloro-benzylamide;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-thiomorpholin-4-yl-1,6-naphthyridine-7-carboxamide;

5-[3-(aminocarbonyl)piperidin-1-yl]-*N*-(3,5-dichlorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

1-(7-{[(3,5-dichlorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)-4-(2-phenylethyl)piperazine;

4-[(7-{[(3,5-dichlorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)amino]pyridine;

5-[(cyclopropylmethyl)amino]-*N*-(3,5-dichlorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-5-{[2-(formylamino)ethyl]amino}-8-hydroxy-1,6-naphthyridine-7-carboxamide;

2-[(7-{[(3,5-dichlorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)amino]ethanamine;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-[(2-methoxyethyl)amino]-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-{[2-(methylthio)ethyl]amino}-1,6-naphthyridine-7-carboxamide;

1-{2-[(7-{[(3,5-dichlorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)amino]ethyl}pyrrolidine;

1 *N*-(3,5-dichlorobenzyl)-8-hydroxy-5-pyrrolidin-1-yl-1,6-naphthyridine-7-carboxamide;

3-{2-[(7-{[(3,5-dichlorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)amino]ethyl}pyridine;

1-{3-[(7-{[(3,5-dichlorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)amino]propyl}-1*H*-imidazoline;

1-{3-[(7-{[(3,5-dichlorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)amino]propyl}pyrrolidine;

1-(2-aminoethyl)-4-(7-{[(3,5-dichlorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)piperazine;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-[(2-phenoxyethyl)amino]-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}-1,6-naphthyridine-7-carboxamide;

2-[benzyl(7-{[(3,5-dichlorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)amino]ethanamine;

1-{3-[(7-{[(3,5-dichlorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)amino]propyl}-4-methylpiperazine;

1:1 mixture of 1-(7-{[(3,5-dichlorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)-1*H*-imidazo[4,5-*b*]pyridine and 3-(7-{[(3,5-dichlorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)-3*H*-imidazo[4,5-*b*]pyridine;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-{[4-(3-methyl-2-oxoimidazolidin-1-yl)phenyl]amino}-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-(1,4,6,7-tetrahydro-5*H*-pyrazolo[4,3-*c*]pyridin-5-yl)-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-({[(2*R*)-5-oxopyrrolidin-2-yl]methyl}amino)-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-{[(5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)methyl]amino}-1,6-naphthyridine-7-carboxamide;

2-(7-{[(3,5-dichlorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)octahydropyrrolo[1,2-*a*]pyrazine;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-[4-(pyrimidin-2-ylamino)piperidin-1-yl]-1,6-naphthyridine-7-carboxamide

2-{2-[(7-{[(3,5-dichlorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)(methyl)amino]ethyl}pyridine;

N-(3,5-dichlorobenzyl)-5-(dimethylamino)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

8-Hydroxy-5-(3-morpholin-4-yl-prop-1-ynyl)-[1,6]naphthyridine-7-carboxylic acid 3,5-dichloro-benzylamide;

N-(3,5-difluorobenzyl)-8-hydroxy-5-(methylsulfonyl)-1,6-naphthyridine-7-carboxamide;

5-cyano-N-(2,3-dimethoxybenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-thien-2-yl-1,6-naphthyridine-7-carboxamide;

8-hydroxy-5-phenylsulfanyl-[1,6]naphthyridine-7-carboxylic acid 2-methylsulfanylbenzylamide;

N-(2,3-dimethoxybenzyl)-8-hydroxy-5-(methylsulfonyl)-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-[(2-hydroxyethyl)amino]-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-(propylamino)-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-[(1H-imidazol-4-ylethyl)amino]-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-[(3-phenylprop-1-yl)amino]-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-[(3-morpholin-4-ylpropyl)amino]-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-[4-(pyridin-2-ylmethyl)piperazin-1-yl]-1,6-naphthyridine-7-carboxamide;

N-(3,5-dichlorobenzyl)-8-hydroxy-5-[(2-morpholin-4-yl-2-pyridin-3-ylethyl)amino]-1,6-naphthyridine-7-carboxamide;

N-(2,3-dimethoxybenzyl)-5-{[4-(dimethylamino)phenyl]thio}-8-hydroxy-1,6-naphthyridine-7-carboxamide;

8-hydroxy-6-methyl-[1,6]naphthyridine-7-carboxylic acid 3,5-dichloro-benzylamide;

8-hydroxy-6-methyl-[1,6]naphthyridine-7-carboxylic acid 4-fluoro-benzylamide;

5-bromo-N-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

1-(7-{[(4-fluorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)-4-methylpiperazine;

1-(7-{[(4-fluorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)piperazine;

5-[[2-(dimethylamino)-2-oxoethyl](methyl)amino]-N-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-1-(7-{[(4-fluorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)-N-1-,N-2-,N-2-trimethylethanediamide ;

N-(4-fluorobenzyl)-5-(2,6-dioxohexahydropyrimidin-4-yl)-8-hydroxy-[1,6]napthyridine-7-carboxamide;

5-(1,3-dimethyl-2,6-dioxohexahydro-4-pyrimidinyl)-N-(4-fluorobenzyl)-8-hydroxy[1,6]-naphthyridine-7-carboxamide;

5-(1-methyl-2,6-dioxohexahydro-4-pyrimidinyl)-N-(4-fluorobenzyl)-8-hydroxy[1,6]-naphthyridine-7-carboxamide;

5-(3-methyl-2,6-dioxohexahydro-4-pyrimidinyl)-N-(4-fluorobenzyl)-8-hydroxy[1,6]-naphthyridine-7-carboxamide;

N-(4-fluorobenzyl)-8-hydroxy-5-(5-oxo-1,4-thiazepan-7-yl)[1,6]naphthyridine-7-carboxamide;

N-(4-fluorobenzyl)-8-hydroxy-5-(1-oxido-5-oxo-1,4-thiazepan-7-yl)-[1,6]naphthyridine-7-carboxamide;

N-(4-fluorobenzyl)-8-hydroxy-5-(1,1-dioxido-5-oxo-1,4-thiazepan-7-yl)[1,6]-naphthyridine-7-carboxamide;

N-(4-fluorobenzyl)-5-{[2-(dimethylamino)-2-oxoethyl]sulfanyl}-8-hydroxy-[1,6]napthyridine-7-carboxamide;

N-(4-fluorobenzyl)-5-[2-(dimethylamino)-2-oxoethoxy]-8-hydroxy-[1,6]napthyridine-7-carboxamide;

N-(4-fluorobenzyl)-5-{[2-(dimethylamino)-2-oxoethyl](methylsulfonyl)amino}-8-hydroxy-[1,6]napthyridine-7-carboxamide;

N-(4-fluorobenzyl)-5-[3-(dimethylamino)-3-oxopropyl]-8-hydroxy-[1,6]napthyridine-7-carboxamide;

N-(4-fluorobenzyl)-5-[(1*E*)-3-(dimethylamino)-3-oxo-1-propenyl]-8-hydroxy-[1,6]napthyridine-7-carboxamide;

N-(4-fluorobenzyl)-5-[2-(3-oxo-1-piperazinyl)ethyl]-8-hydroxy-[1,6]napthyridine-7-carboxamide;

N-(4-fluorobenzyl)-5-[2-(2-oxo-1-imidazolidinyl)ethyl]-8-hydroxy-[1,6]napthyridine-7-carboxamide;

N-(4-fluorobenzyl)-5-[2-(2-oxo-1-piperazinyl)ethyl]-8-hydroxy-[1,6]napthyridine-7-carboxamide;

5-(1,1-dioxido-1,2-thiazinan-2-yl)-*N*-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

5-(1,1-dioxidoisothiazolidin-2-yl)-*N*-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-(4-fluorobenzyl)-8-hydroxy-5-[methyl(methylsulfonyl)amino]-1,6-naphthyridine-7-carboxamide;

5-[acetyl(methyl)amino]-*N*-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

5-[[(dimethylamino)carbonyl](methyl)amino]-*N*-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-(4-fluorobenzyl)-6-hydroxy-3-methyl-1-(2-morpholin-4-ylethyl)-2-oxo-2,3-dihydro-1H-pyrimido[4,5,6-de]-1,6-naphthyridine-5-carboxamide;

N-(4-fluorobenzyl)-8-hydroxy-5-thiomorpholin-4-yl-1,6-naphthyridine-7-carboxamide;

5-(1,1-dioxidothiomorpholin-4-yl)-*N*-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-(4-fluorobenzyl)-8-hydroxy-5-(4-methyl-3-oxopiperazin-1-yl)-1,6-naphthyridine-7-carboxamide;

1-(7-{[4-fluorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl-L-prolinamide;

N-(4-fluorobenzyl)-8-hydroxy-5-(2-oxotetrahydropyrimidin-1(2*H*)-yl)-1,6-naphthyridine-7-carboxamide;

N-(4-fluorobenzyl)-8-hydroxy-5-(2-oxoimidazolidin-1-yl)-1,6-naphthyridine-7-carboxamide;

N-7-(4-fluorobenzyl)-8-hydroxy-*N* 5, *N* 5-dimethyl-1,6-naphthyridine-5,7-dicarboxamide;

N 7-(4-fluorobenzyl)-8-hydroxy-*N* 5-isopropyl-*N* 5-methyl-1,6-naphthyridine-5,7-dicarboxamide;

N 7-(4-fluorobenzyl)-8-hydroxy-*N* 5-(2-morpholin-4-ylethyl)-1,6-naphthyridine-5,7-dicarboxamide;

N 5-[2-(dimethylamino)-2-oxoethyl]-*N* 7-(4-fluorobenzyl)-8-hydroxy-*N* 5-methyl-1,6-naphthyridine-5,7-dicarboxamide;

N-(4-fluorobenzyl)-5-(1,1-dioxido-4-oxo-1,2,5-thiadiazepan-2-yl)-8-hydroxy-[1,6]napthyridine-7-carboxamide;

N-(4-fluorobenzyl)-5-(1,1-dioxido-5-methyl-4-oxo-1,2,5-thiadiazepan-2-yl)-8-hydroxy-[1,6]napthyridine-7-carboxamide;

N-(4-fluorobenzyl)-5-(1,1-dioxido-5-ethyl-4-oxo-1,2,5-thiadiazepan-2-yl)-8-hydroxy-[1,6]napthyridine-7-carboxamide;

N-(4-fluorobenzyl)-5-(1,1-dioxido-1,5,2-dithiazepan-2-yl)-8-hydroxy-[1,6]napthyridine-7-carboxamide;

N-(4-fluorobenzyl)-5-(1,1,5,5-tetraoxido-1,5,2-dithiazepan-2-yl)-8-hydroxy-[1,6]napthyridine-7-carboxamide;

N-(4-fluorobenzyl)-5-(1,4-dimethyl-7-oxo-1,4-diazepan-5-yl)-8-hydroxy-[1,6]-napthyridine-7-carboxamide;

N-(4-fluorobenzyl)-5-(1-methyl-7-oxo-1,4-diazepan-5-yl)-8-hydroxy-[1,6]-napthyridine-7-carboxamide;

N-(4-Fluorobenzyl)-5-(7-oxo-1,4-diazepan-5-yl)-8-hydroxy-[1,6]-napthyridine-7-carboxamide

N-(4-fluorobenzyl)-5-[4-(methylsulfonyl)thiomorpholin-2-yl]-8-hydroxy-[1,6]napthyridine-7-carboxamide;

N-(4-fluorobenzyl)-5-[4-(methylsulfonyl)-1-oxidothiomorpholin-2-yl]-8-hydroxy-[1,6]napthyridine-7-carboxamide;

N-(4-fluorobenzyl)-5-[4-(methylsulfonyl)-1,1-dioxidothiomorpholin-2-yl]-8-hydroxy-[1,6]napthyridine-7-carboxamide;

N-(4-fluorobenzyl)-5-(2-Acetyl-1-methylpyrazolidin-3-yl)-8-hydroxy-[1,6]napthyridine-7-carboxamide;

N-(4-fluorobenzyl)-5-(1,1-dioxido-1,2,5-thiadiazepan-2-yl)-8-hydroxy-[1,6]napthyridine-7-carboxamide;

N-(4-fluorobenzyl)-8-hydroxy-5-[5-(methylsulfonyl)-1,1-dioxido-1,2,5-thiadiazepan-2-yl]-1,6-naphthyridine-7-carboxamide;

N-(4-fluorobenzyl)-8-hydroxy-5(6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2yl)-1,6-naphthyridine-7-carboxamide;

N-(4-fluorobenzyl)-8-hydroxy-5-{methyl[(1-methyl-1*H*-imidazol-4-yl)sulfonyl]amino}-1,6-naphthyridine-7-carboxamide;

N-[4-fluoro-2-(methylsulfonyl)benzyl]-8-hydroxy-5-{methyl[(1-methyl-1*H*-imidazol-4-yl)sulfonyl]amino}-1,6-naphthyridine-7-carboxamide;

N-7-[4-fluoro-2-(methylsulfonyl)benzyl]-8-hydroxy-N-5-,N-5-dimethyl-1,6-naphthyridine-5,7-dicarboxamide;

N-[4-fluoro-2-(methylsulfonyl)benzyl]-8-hydroxy-5-(1,1-dioxido-1,2-thiazinan-2-yl)-1,6-naphthyridine-7-carboxamide

N-(2-(methylsulfonyl)benzyl)-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-(2-[(dimethylaminosulfonyl]-4-fluorobenzyl)-5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-(4-fluorobenzyl)-8-hydroxy-5-(1-methyl-5-oxopyrrolidin-3-yl)-1,6-naphthyridine-7-carboxamide;

and pharmaceutically acceptable salts thereof.

Other embodiments of the present invention include the following:

(a) A pharmaceutical composition comprising a compound of Formula (I) and a pharmaceutically acceptable carrier.

(b) The pharmaceutical composition of (a), further comprising at least one antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse transcriptase inhibitors.

(c) A method of inhibiting HIV integrase in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of a compound of Formula (I).

(d) A method of preventing or treating infection by HIV in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of a compound of Formula (I).

(e) The method of (d), wherein the compound of Formula (I) is administered in combination with a therapeutically effective amount of at least one antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse transcriptase inhibitors.

(f) A method of preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of a compound of Formula (I).

(g) The method of (f), wherein the compound is administered in combination with a therapeutically effective amount of at least one antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse transcriptase inhibitors

(h) A method of inhibiting HIV integrase in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of the composition of (a) or (b).

(i) A method of preventing or treating infection by HIV in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of the composition of (a) or (b).

(j) A method of preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of the composition of (a) or (b).

Still other embodiments of the present invention include the following:

(k) A pharmaceutical composition which comprises the product prepared by combining (e.g., mixing) an effective amount of a compound of Formula (I) and a pharmaceutically acceptable carrier.

(l) A combination useful for inhibiting HIV integrase, for treating or preventing infection by HIV, or for preventing, treating or delaying the onset of AIDS, which is a therapeutically effective amount of a compound of Formula (I) and a therapeutically effective amount of an HIV infection/AIDS treatment agent selected from the group consisting of HIV/AIDS antiviral agents, immunomodulators, and anti-infective agents.

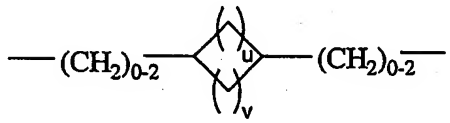
(m) The combination of (l), wherein the HIV infection/AIDS treatment agent is an antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors and nucleoside HIV reverse transcriptase inhibitors.

Additional embodiments of the invention include the pharmaceutical compositions and methods set forth in (a)-(j) above and the compositions and combinations set forth in (k)-(m), wherein the compound employed therein is a compound of one of the embodiments, classes, or aspects of compounds described above. In all of these embodiments, the compound may optionally be used in the form of a pharmaceutically acceptable salt.

As used herein, the term "C_{1-6} alkyl" (or "C_1-C_6 alkyl") means linear or branched chain alkyl groups having from 1 to 6 carbon atoms and includes all of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. "C_{1-4} alkyl" means n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl.

The term "C_0" as employed in expressions such as "C_{0-6} alkyl" means a direct covalent bond. Similarly, when an integer defining the presence of a certain number of ring atoms in a cyclic group is equal to zero, it means that the ring atoms

adjacent thereto in the cyclic group are connected directly by a bond. For example, when L is



wherein u and v are each integers having a value from 0 to 4, provided that the sum of u + v is 1, 2, 3 or 4, L has the following structure when u is 1 and v is zero:

The term "C_{2-5} alkenyl" (or "C_2-C_5 alkenyl") means linear or branched chain alkenyl groups having from 2 to 5 carbon atoms and includes all of the pentenyl isomers as well as 1-butenyl, 2-butenyl, 3-butenyl, isobutenyl, 1-propenyl, 2-propenyl, and ethenyl (or vinyl). Similar terms such as "C_{2-3} alkenyl" have an analogous meaning.

The term "C_{2-5} alkynyl" (or "C_2-C_5 alkynyl") means linear or branched chain alkynyl groups having from 2 to 5 carbon atoms and includes all of the pentynyl isomers as well as 1-butynyl, 2-butynyl, 3-butynyl, 1-propynyl, 2-propynyl, and ethynyl (or acetylenyl). Similar terms such as "C_{2-3} alkynyl" have an analogous meaning.

The term "C_{3-7} cycloalkyl" (or "C_3-C_7 cycloalkyl") means a cyclic ring of an alkane having three to seven total carbon atoms (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl). The term "C_{3-6} cycloalkyl" refers to a cyclic ring selected from cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Terms such as "C_3-C_5 cycloalkyl" have an analogous meaning.

The term "halogen" (or "halo") refers to fluorine, chlorine, bromine and iodine (alternatively, fluoro, chloro, bromo, and iodo).

The term "thio" (also referred to as "thioxo") means divalent sulfur; i.e., =S.

The term "C_{1-6} haloalkyl" (which may alternatively be referred to as "C_1-C_6 haloalkyl" or "halogenated C_1-C_6 alkyl") means a C_1 to C_6 linear or branched alkyl group as defined above with one or more halogen substituents. The term "C_{1-4} haloalkyl" has an analogous meaning.

The term "C_{1-6} fluoroalkyl" (which may alternatively be referred to as "C_1-C_6 fluoroalkyl" or "fluorinated C_1-C_6 alkyl") means a C_1 to C_6 linear or

branched alkyl group as defined above with one or more fluorine substituents. The term "C_1-4 fluoroalkyl" (or "C_1-C_4 fluoroalkyl" or "fluorinated C_1-C_4 alkyl") has an analogous meaning. Representative examples of suitable fluoroalkyls include the series $(CH_2)_{0-4}CF_3$ (i.e., trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoro-n-propyl, etc.), 1-fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 3,3,3-trifluoroisopropyl, 1,1,1,3,3,3-hexafluoroisopropyl, and perfluorohexyl.

The term "aryl" refers to aromatic mono- and poly-carbocyclic ring systems, wherein the individual carbocyclic rings in the polyring systems may be fused or attached to each other via a single bond. Suitable aryl groups include, but are not limited to, phenyl, naphthyl, and biphenylenyl.

The term "heterocycle" (and variations thereof such as "heterocyclic" or "heterocyclyl") broadly refers to a 4- to 8-membered monocyclic ring, 7- to 12-membered bicyclic ring system, or an 11 to 16-membered tricyclic ring system, any ring of which is saturated or unsaturated, and which consists of carbon atoms and one or more heteroatoms selected from N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heterocyclic ring may be attached at any heteroatom or carbon atom, provided that attachment results in the creation of a stable structure. When the heterocyclic ring has substituents, it is understood that the substituents may be attached to any atom in the ring, whether a heteroatom or a carbon atom, provided that a stable chemical structure results. Representative examples of heterocyclics include piperidinyl, piperazinyl, azepinyl, pyrrolyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolidinyl, triazolyl, tetrazolyl, imidazolinyl, pyridyl (or pyridinyl), pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiomorpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinoxazolinyl, isothiazolidinyl, quinolinyl, isoquinolinyl, benzimidazolyl, thiadazolyl, benzopyranyl, benzothiazolyl, benzoazolyl, furyl (or furanyl), tetrahydrofuryl (or tetrahydrofuranyl), tetrahydropuranyl, thienyl (alternatively thiophenyl), benzothiophenyl, oxadiazolyl, and benzo-1,3-dioxacyclopentyl (alternatively, 1,3-benzodioxolyl). Representative examples of heterocyclics also include the following bicyclics: indolyl, benzotriazolyl, imidazo[4,5-b]pyridinyl, dihydroimidazo[4,5-b]pyridinyl, pyrazolo[4,3-c]pyridinyl, dihydropyrazolo[4,3-c]pyridinyl, tetrahydropyrazolo[4,3-c]pyridinyl, pyrrolo[1,2-a]pyrazinyl, dihydropyrrolo[1,2-a]pyrazinyl, tetrahydropyrrolo[1,2-a]pyrazinyl,

octahydropyrrolo[1,2-a]pyrazinyl, isoindolyl, indazolyl, indolinyl, isoindolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, chromanyl, and isochromanyl.

Representative examples of heterocyclics also include the following saturated monocyclics: hexahydropyrimidinyl, thiazinanyl (e.g., 1,2-thiazinanyl, alternatively named tetrahydro-1,2-thiazinyl), thiazepanyl (e.g., 1,4-thiazepanyl, alternatively named hexahydro-1,4-thiazepinyl), azepanyl (alternatively hexahydroazepinyl), thiadiazepanyl (e.g., 1,2,5-thiadiazepanyl), dithiazepanyl (e.g., , 1,5,2,-dithiazepanyl), diazepanyl (e.g., 1,4-diazepanyl), and thiadiazinanyl (e.g., 1,2,6-thiadiazinanyl).

The term "heteromonocycle" (and variations thereof such as "heteromonocyclyl" or "heteromonocyclic") refers to a to a 4- to 8-membered monocyclic ring which is saturated or unsaturated, and which consists of carbon atoms and one or more heteroatoms selected from N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heterocyclic ring may be attached at any heteroatom or carbon atom, provided that attachment results in the creation of a stable structure. Representative examples of monoheterocycles are disclosed above.

The term "heteroaromatic ring" refers to a monocyclic heterocycle as defined above which is an aromatic heterocycle. Representative examples of heteroaromatics include pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl (or thiophenyl), thiazolyl, furanyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isooxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, and thiadiazolyl.

Unless expressly set forth to the contrary, an "unsaturated" ring is a partially or fully unsaturated ring. For example, an "unsaturated monocyclic C_6 carbocycle" refers to cyclohexene, cyclohexadiene, and benzene.

The present invention also includes a compound of the present invention for use in (a) inhibiting HIV protease, (b) preventing or treating infection by HIV, or (c) preventing, treating or delaying the onset of AIDS or ARC. The present invention also includes the use of a compound of the present invention as described above as a medicament for (a) inhibiting HIV integrase, (b) preventing or treating infection by HIV, or (c) preventing, treating or delaying the onset of AIDS or ARC.

The compounds of the present invention may have asymmetric centers and may occur, except when specifically noted, as mixtures of stereoisomers or as

individual diastereomers, or enantiomers, with all isomeric forms being included in the present invention.

When any variable (e.g., R^a, R^b, R^c, R^k, etc.) occurs more than one time in any constituent or in Formula I or in any other formula depicting and describing compounds of the invention, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

The term "substituted" (e.g., as in "phenyl ring, unsubstituted or substituted with from 1 to 5 substituents ...") includes mono- and poly-substitution by a named substituent to the extent such single and multiple substitution is chemically allowed. For example, a carbocycle or heterocycle substituted with more than one substituent can have multiple substituents on the same ring atom to the extent it is chemically permitted. A ring sulfur atom in a saturated heterocycle can, for example, typically be substituted with 1 (-S(=O)-) or 2 oxo groups ($-SO_2-$).

The compounds of the present invention may be administered in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" is intended to include all acceptable salts which can be used as a dosage form for modifying the solubility or hydrolysis characteristics or can be used in sustained release or pro-drug formulations. Also, in the case of an acid (-COOH) or alcohol group being present, pharmaceutically acceptable esters can be employed, e.g. acetate, maleate, pivaloyloxymethyl, and the like, and those esters known in the art for modifying solubility or hydrolysis characteristics for use as sustained release or prodrug formulations.

The compounds of the present invention may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in dosage unit formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention each mean providing the compound or a prodrug of the compound to the individual in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., antiviral agents useful for treating HIV

infection or AIDS), "administration" and its variants are each understood to include concurrent and sequential provision of the compound or prodrug thereof and other agents.

The term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combining the specified ingredients in the specified amounts.

By "pharmaceutically acceptable" is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The term "subject," (alternatively referred to herein as "patient") as used herein refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease being treated. When the active compound (i.e., active ingredient) is administered as the salt, references to the amount of active ingredient are to the free acid or free base form of the compound.

The compounds of this invention can be administered orally to humans in a dosage range of 0.1 to 1000 mg/kg body weight in divided doses. One preferred dosage range is 0.1 to 200 mg/kg body weight orally in divided doses. Another preferred dosage range is 0.5 to 100 mg/kg body weight orally in divided doses. It will be understood that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

The present invention is also directed to combinations of the HIV integrase inhibitor compounds with one or more agents useful in the treatment of HIV infection or AIDS. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in

combination with effective amounts of one or more HIV/AIDS antivirals, imunomodulators, antiinfectives, or vaccines useful for treating HIV infection or AIDS, such as those disclosed in Table 1 of WO 01/38332. In one embodiment, the compounds of this invention may be effectively administered in combination with effective amounts of one or more HIV/AIDS antivirals selected from the group consisting of amprenavir, abacavir, delaviridine, dideoxycytidine (ddC), dideoxyinosine (ddI), efavirenz, indinavir, lamivudine (3TC), nelvinavir, nevirapine, ritonavir, saquinavir, stavudine (d4T), zidovudine (AZT), lopinavir, Kaletra (lopinavir and ritonavir), zalcitabine, trizivir (abacavir, lamibudine and zidovudine), and tipranavir. It will be understood that the scope of combinations of the compounds of this invention with HIV/AIDS antivirals is not limited to the list in the preceding sentence, but includes in principle any combination with any pharmaceutical composition useful for the treatment of HIV infection or AIDS. When employed in combination with the compounds of the invention, the HIV/AIDS antivirals and other agents are typically employed in their conventional dosage ranges and regimens as reported in the art, including the dosages described in the Physicians' Desk Reference, 54th edition, Medical Economics Company, 2000. The dosage ranges for a compound of the invention in these combinations are the same as those set forth above.

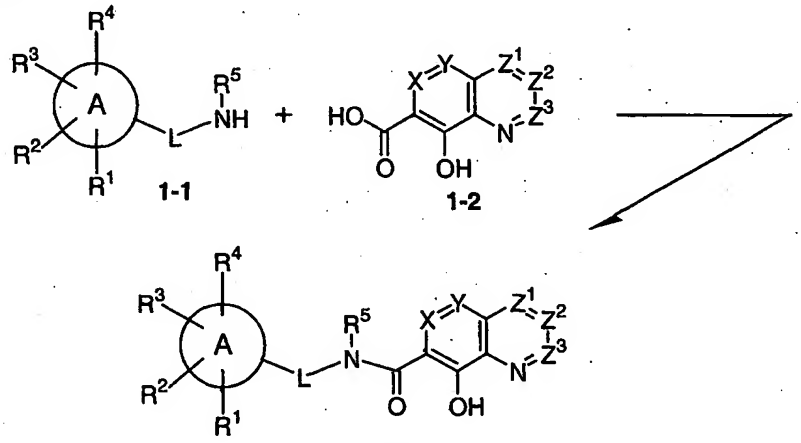
Abbreviations used in the instant specification, particularly the Schemes and Examples, include the following:
Ac = acetyl; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DEAD = diethylazodicarboxylate; DMF = N,N-dimethylformamide; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone; DMSO = dimethylsulfoxide; EDC = 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide; EDTA = ethylenediaminetetraacetic acid; ES MS = electrospray mass spectrometry; Et = ethyl
EtOAc = ethyl acetate; EtOH = ethanol; FAB HRMS = fast atom bombardment high resolution mass spectroscopy; FAB MS = fast atom bombardment mass spectroscopy; HOBt = 1-hydroxy benzotriazole hydrate; HPLC = high performance liquid chromatography; *i*-Pr = isopropyl; Me = methyl; MsCl = methanesulfonyl chloride (or mesyl chloride); NBS = N-bromosuccinimide; NIS = N-iodosuccinimide; NMR = nuclear magnetic resonance; Ph = phenyl; PMBCl = *p*-methoxybenzyl chloride
rt and RT = room temperature; TFA = trifluoroacetic acid; THF = tetrahydrofuran.

The compounds of the present invention can be readily prepared according to the following reaction schemes and examples, or modifications thereof,

using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. Furthermore, other methods for preparing compounds of the invention will be readily apparent to the person of ordinary skill in the art in light of the following reaction schemes and examples. Unless otherwise indicated, all variables are as defined above.

The compounds of the present invention can be prepared by the coupling of suitable (poly)azanaphthenyl carboxylic acids (or acid derivatives such as acid halides or esters) with the appropriate amines, as represented by the following general scheme:

SCHEME 1



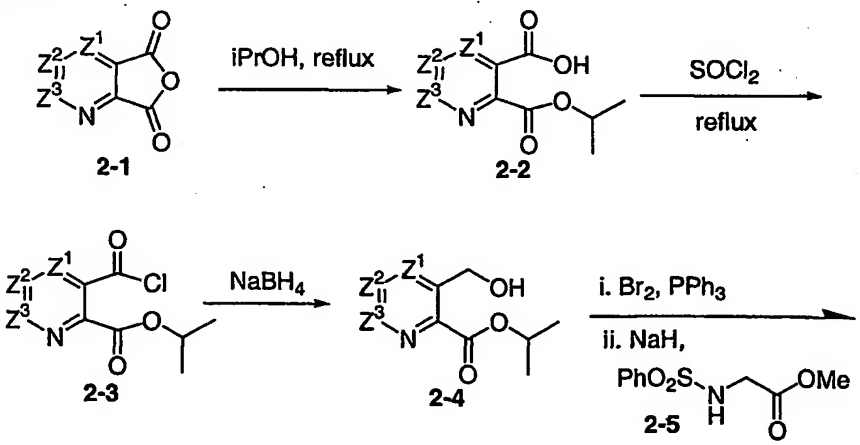
Methods for coupling carboxylic acids with amines to form carboxamides are well known in the art. Suitable methods are described, for example, in Jerry March, Advanced Organic Chemistry, 3rd edition, John Wiley & Sons, 1985, pp. 370-376. Amines of formula **1-1** can be prepared using the methods described in Richard Larock, Comprehensive Organic Transformations, VCH Publishers Inc, 1989, pp 385-438, or routine variations thereof. Azanaphthenyl and polyazanaphthenyl carboxylic acids of formula **1-2** can be prepared using methods described in Ochiai et al., *Chem.Ber.* 1937, 70: 2018, 2023; Albert et al., *J.Chem.Soc.* 1952, 4985, 4991; and

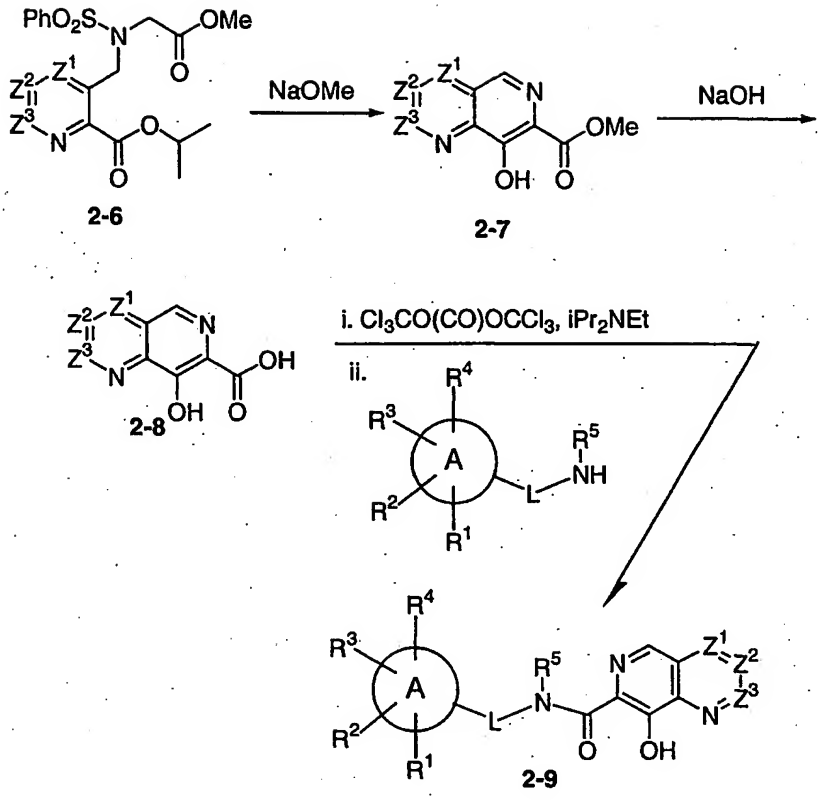
Barlin et al., *Aust.J.Chem.* 1990, 43: 1175-1181; or routine variations thereof. Schemes 2-16 below illustrate and expand upon the chemistry portrayed in Scheme 1.

In Scheme 2, following the procedure set forth in Ornstein et al., *J. Med. Chem.* 1989, 32: 827-833, a cyclic anhydride such as quinolinic anhydride (i.e., $Z^1 = Z^2 = Z^3 = CH$ in **2-1**) can be opened with isopropanol to provide mono acid **2-2**, which can be converted to the corresponding acyl chloride **2-3** (e.g., by refluxing thionyl chloride). Acyl chloride **2-3** can then be reduced (e.g., with $NaBH_4$ or $LiBH_4$) to the corresponding alcohol **2-4**, which can be converted to the corresponding bromide through the action of bromine in the presence of triphenylphosphine. Alkylation of the bromide with the sodium anion of phenylsulfonamide **2-5** in a polar aprotic solvent like DMF can provide sulfonamide **2-6**, which can be treated with a base (e.g., alkali metal alkoxide such as sodium methoxide) to provide the bicyclic ester **2-7** via a Dieckmann cyclization. Saponification of the ester (e.g., with aqueous NaOH at reflux) will afford the acid **2-8**. The acid **2-8** can be activated with triphosgene and coupled with a variety of amines to provide the compounds of the invention **2-9**.

The starting anhydrides of formula **2-1** can be prepared via methods described in Philips et al., *Justus Liebigs Ann. Chem.* 1895, 288: 2535; Bernthsen et al., *Chem.Ber.* 1887; 20: 1209; Bly et al., *J.Org.Chem.* 1964, 29: 2128-2135; and Krapcho et al., *J.Heterocycl.Chem.* 1993, 30: 1597-1606; or routine variations thereof.

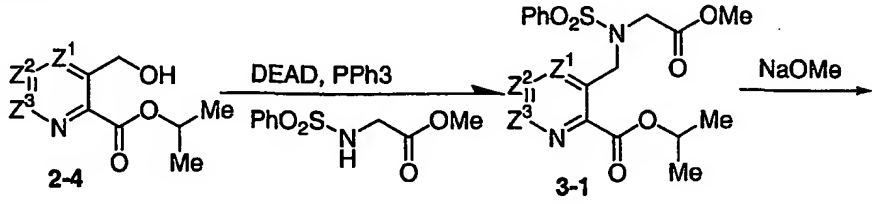
SCHEME 2

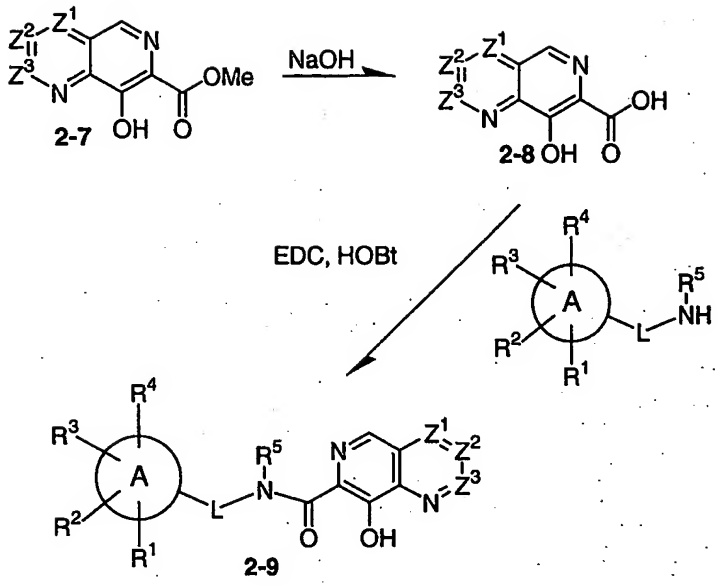




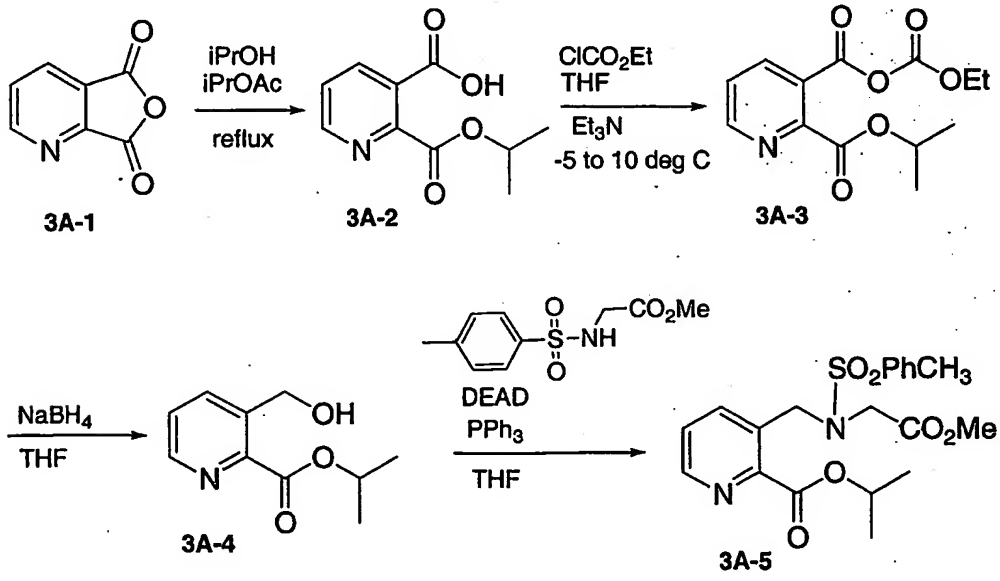
Scheme 3 depicts an alternative synthesis in which alcohol **2-4** can undergo the Mitsunobu reaction with the phenylsulfonamide of glycine methyl ester to provide **3-1**. The sulfonamide **3-1** can again be elaborated to provide the acid **2-8**, which can be coupled with a variety of amines using standard reagents to provide the compounds of the invention **2-9**.

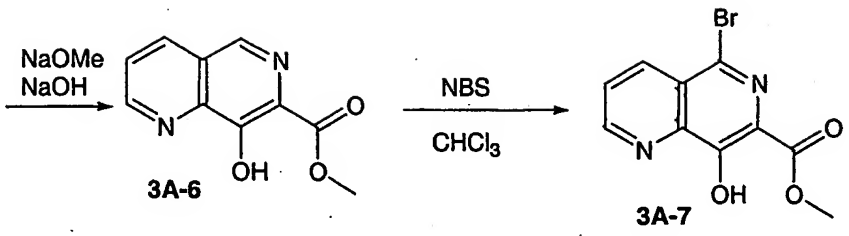
SCHEME 3





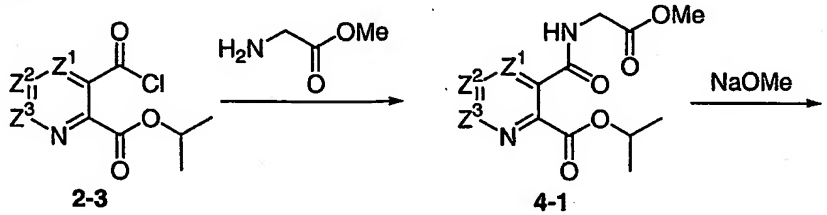
Scheme 3A depicts (for a napthyridine core) a variation of the synthesis shown in Scheme 3, wherein the acid **3A-2** is reacted with ethyl chloroformate to form the mixed anhydride **3A-3**, which is reduced to alcohol **3A-4**.

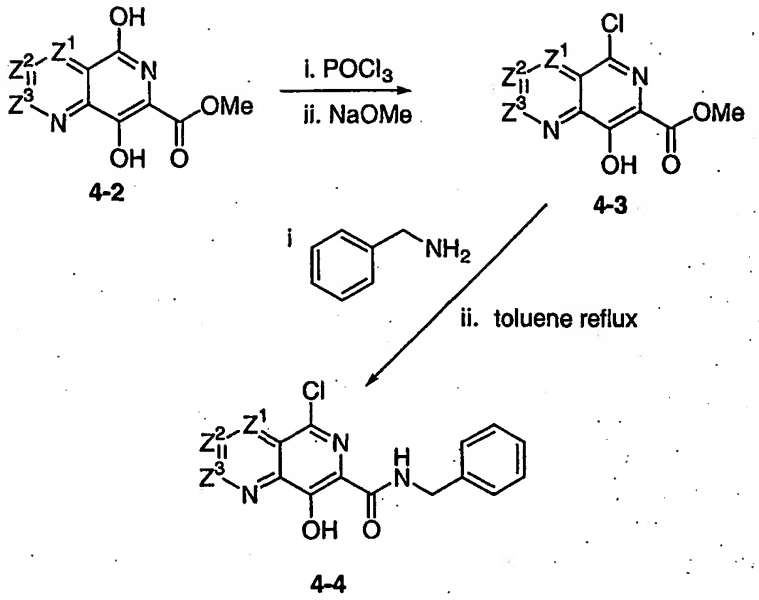




Halogen substituted compounds of the present invention can be prepared as shown in Scheme 4. The acid chloride **2-3** can be reacted with glycine methyl ester to provide the amide **4-1**. Dieckmann cyclization of the ester **4-1** with a sodium alkoxide base in an alcoholic solvent like methanol will provide phenol **4-2**., which can be reacted with phosphorous oxychloride, followed by methanolysis of the intermediate phosphonate esters to provide **4-3**. The ester bond of **4-3** can react selectively with suitable amines in refluxing nonpolar aromatic solvents (e.g., benzylamine refluxed in toluene is depicted in Scheme 4) to provide the corresponding halogenated derivative **4-4**.

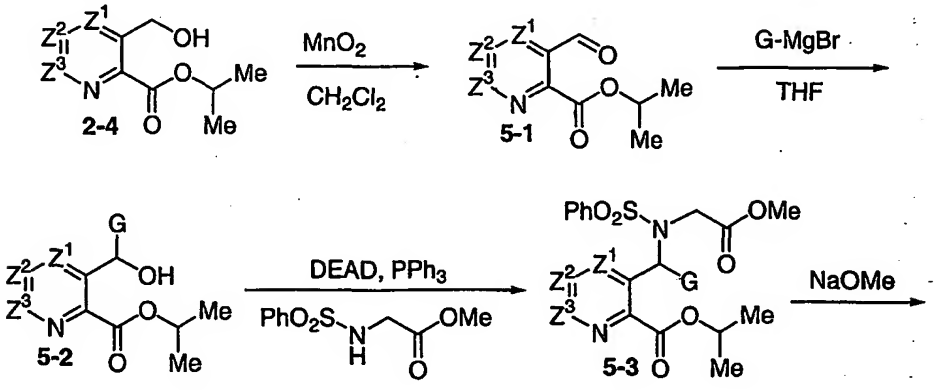
SCHEME 4

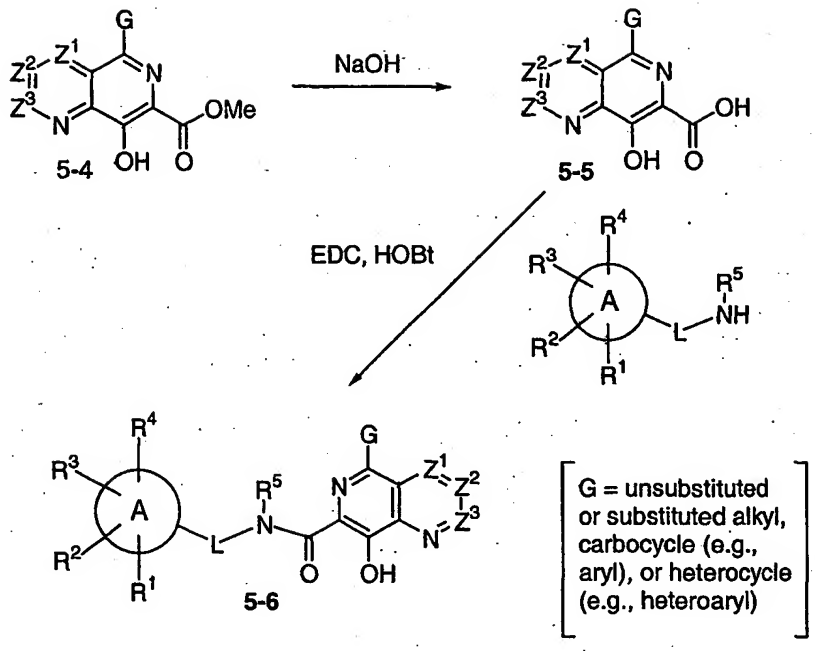




The preparation of compounds that feature additional substituents can be achieved as shown in Scheme 5. Oxidation of the alcohol **2-4** with manganese dioxide in an inert solvent such as methylene chloride will provide aldehyde **5-1**. The addition of Grignard reagents (such as phenyl magnesium bromide) to aldehyde moiety **5-1** can occur regioselectively to provide the alcohol **5-2**, which can then be elaborated to the compounds of the invention **5-6**.

SCHEME 5

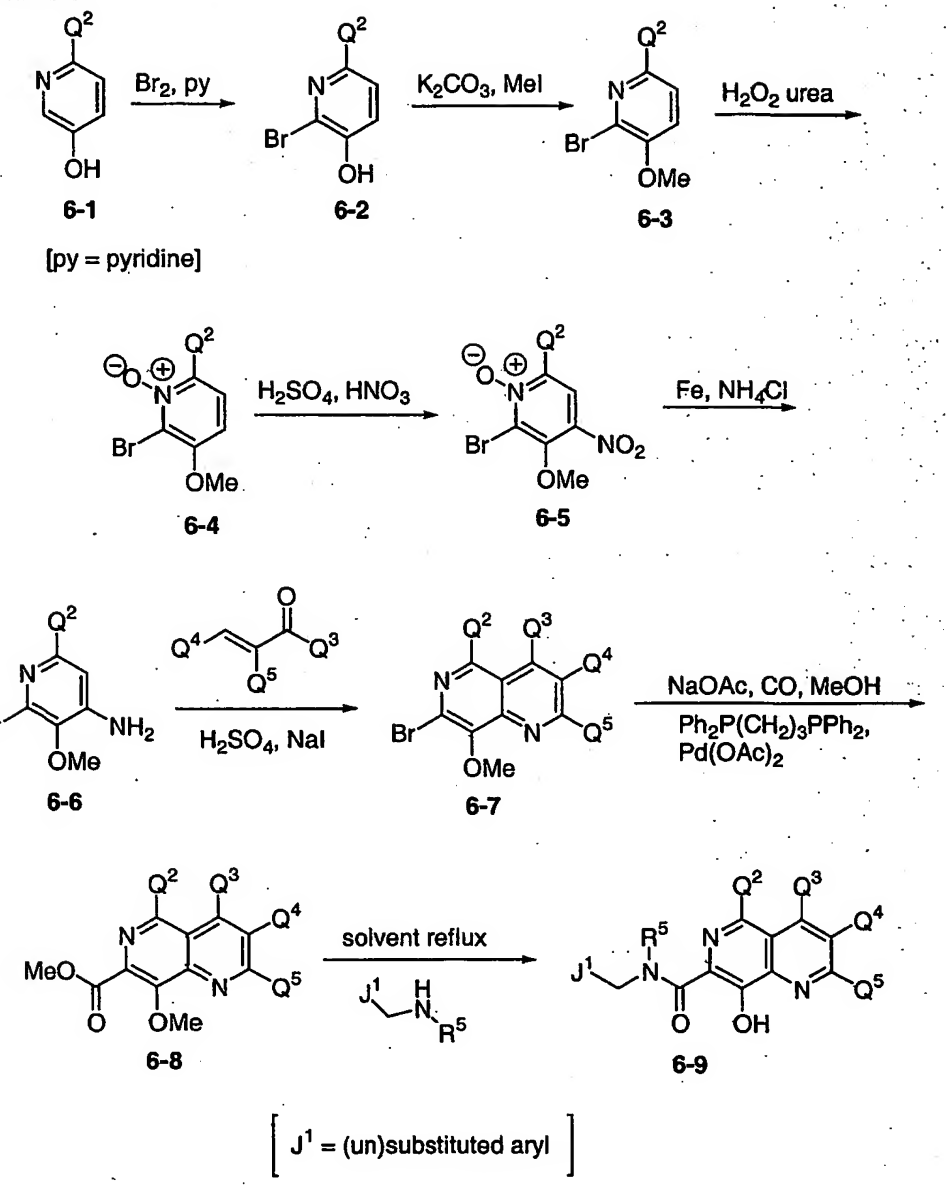




A further synthetic route to prepare compounds that are the subject of the invention is shown in Scheme 6. This methodology allows access to naphthyridine derivatives that are substituted at the 2, 3, 4 and 5 positions. Briefly, a 2-substituted 5-hydroxypyridine derivative **6-1** can be treated with bromine to undergo bromination at the 6 position to afford **6-2**, which can be converted to the methoxypyridine **6-3** and then oxidized to the corresponding N-oxide **6-4**. The N-oxide can be nitrated to provide **6-5**. Reduction of **6-5** with iron in the presence of ammonium chloride can provide the aniline **6-6**, which can be reacted with an alpha,beta-unsaturated aldehyde or ketone in the presence of an acid catalyst like sulfuric acid to provide **6-7** via an annulation. The bromide **6-7** can be elaborated to the amide **6-9** via a sequence of carbonylation and amidation reactions.

2-Substituted 5-hydroxypyridine derivatives of formula **6-1** can be prepared via methods described in Sorm et al., *Collect.Czech.Chem..Commun.*.1949, 14: 331,342; and Saksena et al., *Tetrahedron Lett.*1993, 34: 3267-3270: or routine variations thereof.

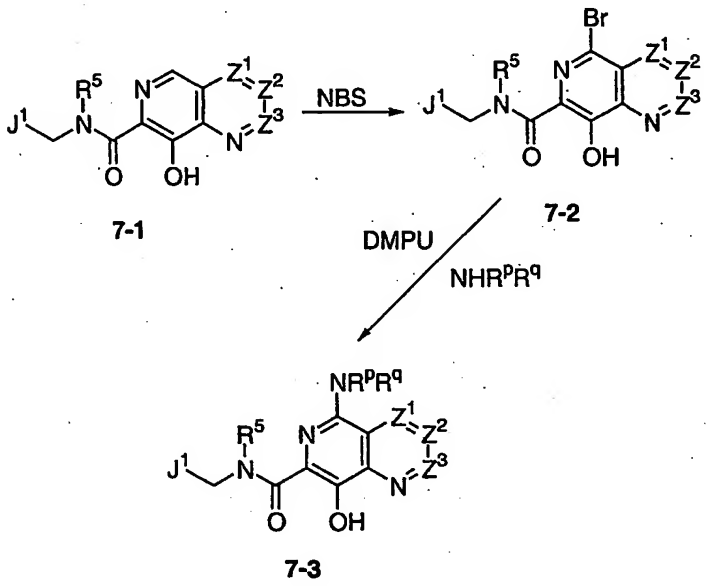
SCHEME 6



Compounds of the invention that comprise an amino substituent at the 5 position can be prepared in the manner set forth in Schemes 7 and 8. Bromination of the phenol **7-1** occurs regioselectively upon treatment with NBS in an inert solvent like methylene chloride to afford **7-2**. Reaction of this bromide with an amine at

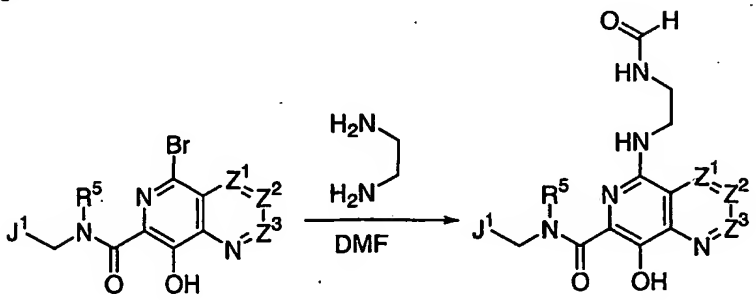
elevated temperatures in the presence of a polar solvent such as DMPU affords compounds of the invention **7-3**. Similar reaction of the bromide **7-2** (Scheme 8) with a diamine such as ethylene diamine in DMF as solvent will afford the formylated derivative **8-1** in addition to the expected diaminoethane derivative.

SCHEME 7



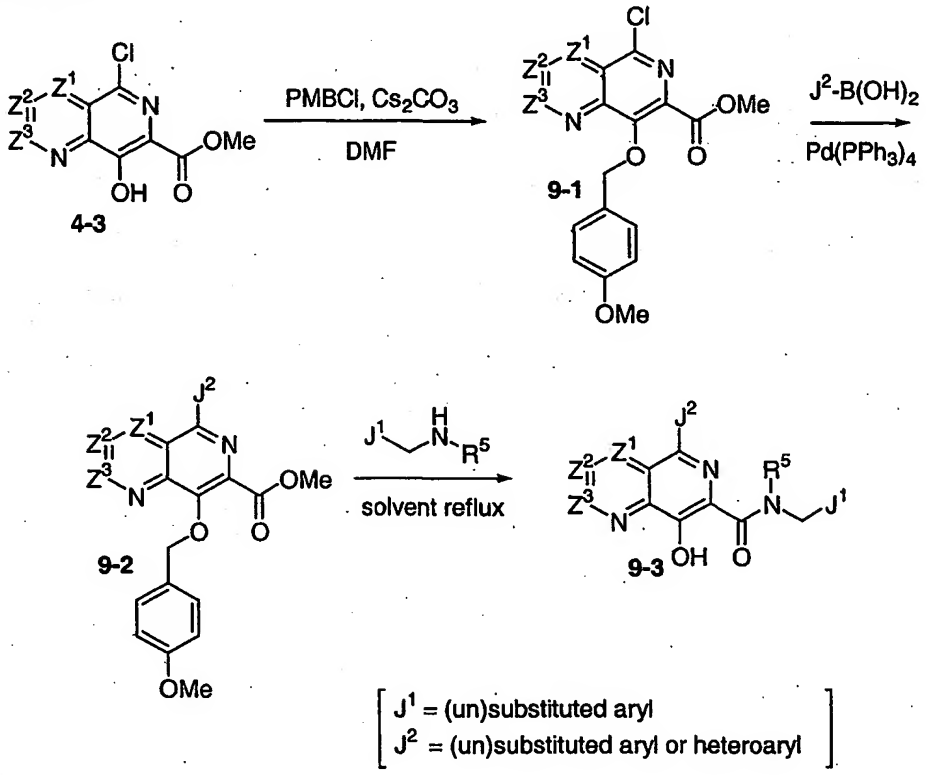
[J^1 = (un)substituted aryl
R^p, R^q = H; alkyl; alkyl substituted with, e.g., OH, alkoxy, carbocycle, or heterocycle; (un)substituted carbocycle, or (un)substituted heterocycle]

SCHEME 8



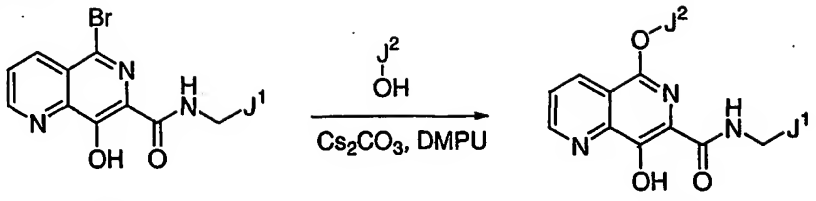
Preparation of aryl and heteroaryl derivatives via palladium cross coupling of the chloride **9-1** and the requisite boronic acids are depicted in Scheme 9.

SCHEME 9

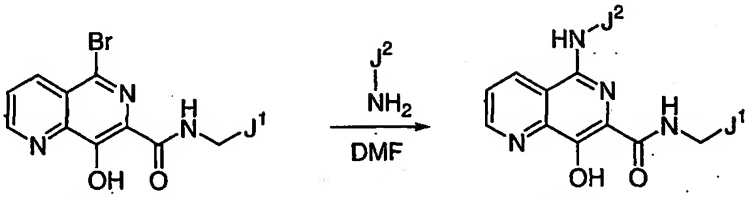


(Hetero)aryloxy, (hetero)arylamino, and (heteroaryl)thioxy derivatives **10-2**, **11-2**, and **12-2** respectively can be prepared as shown in Schemes 10 to 12, which exemplify the procedure for the naphthyridine core. The corresponding sulfone derivatives **12-2** can be obtained by oxidation of the sulfides **12-1** with either ozone or 3-chloroperbenzoic acid as shown in Scheme 12.

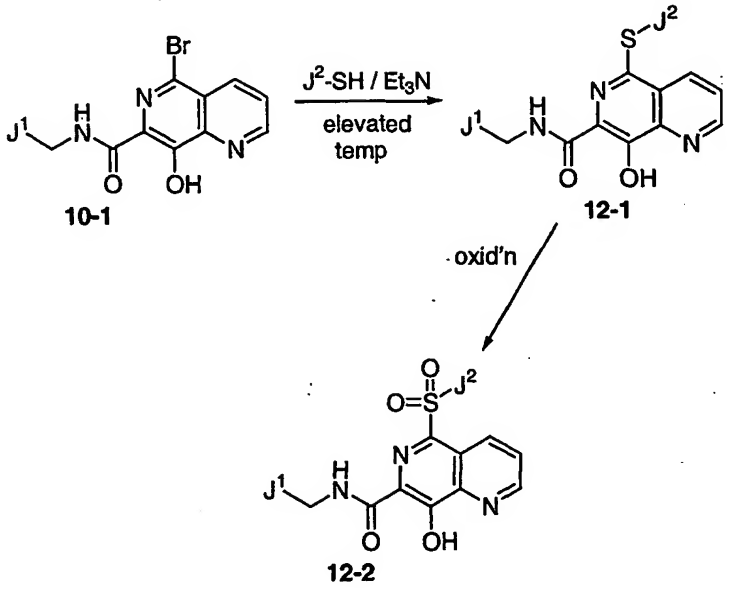
SCHEME 10



SCHEME 11



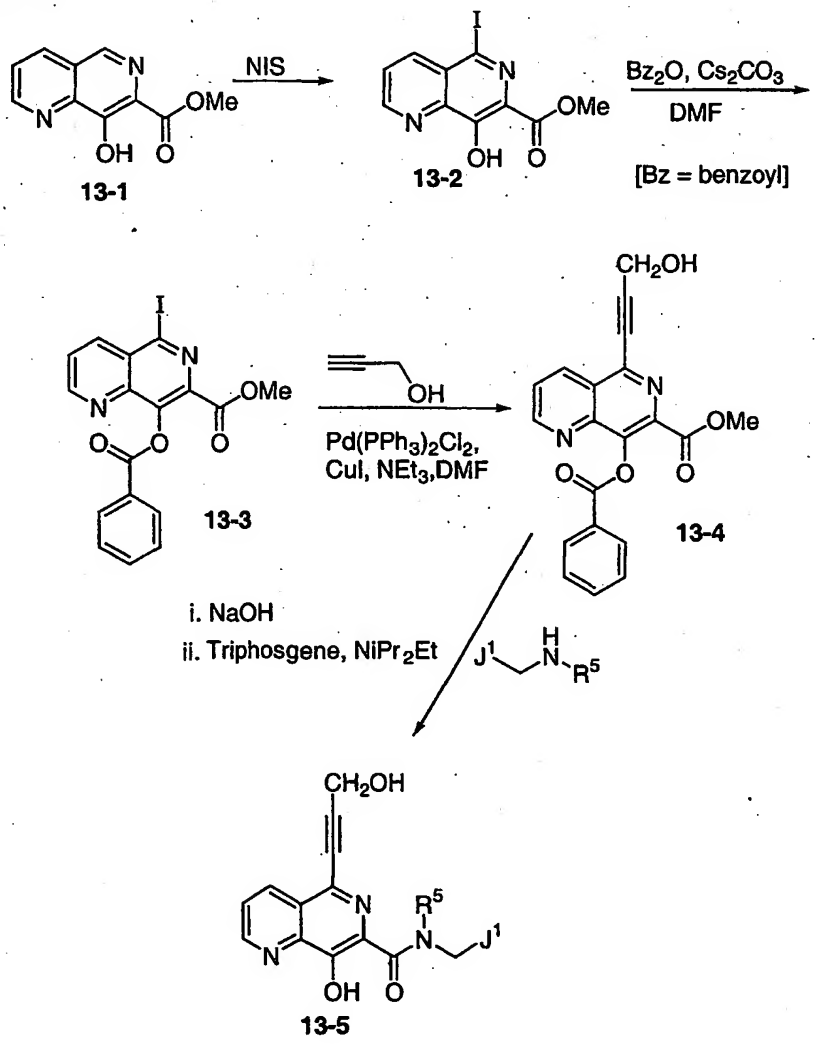
SCHEME 12



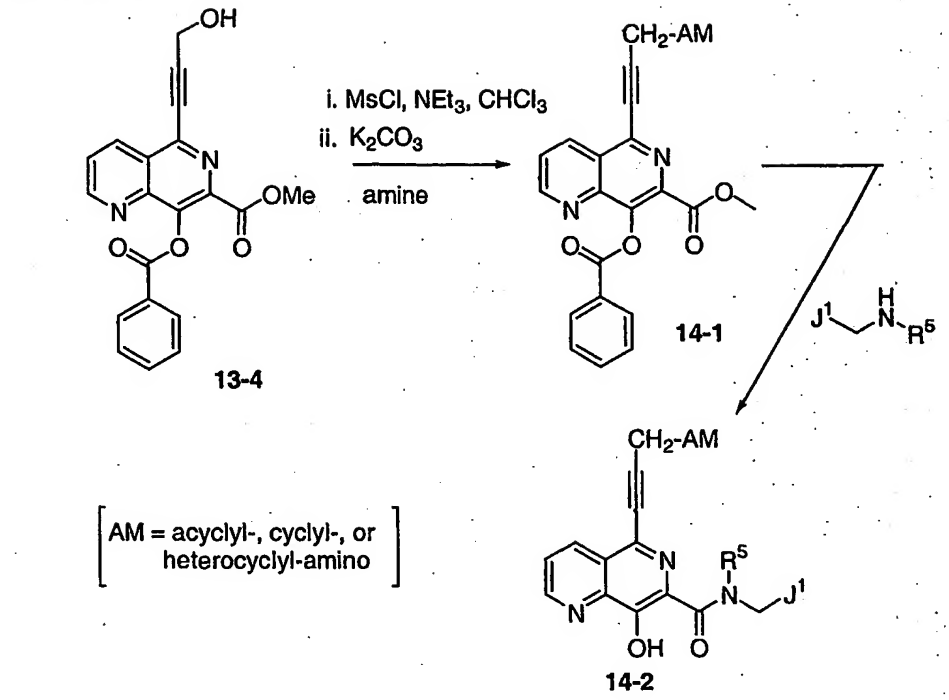
Preparation of compounds of the invention substituted with an acetylene can be prepared according to Scheme 13, which exemplifies the procedure for the naphthyridine core. Following protection of the iodide **13-2** as its benzoate **13-3**, the acetylenic group (for example propynol) can be appended by employing a

suitable palladium catalyst in the presence of copper iodide. Aminolysis of the ester **13-4** will afford the amide **13-5** with concomitant deprotection of the benzoate ester. Alternately the ester **13-4** can be converted to the corresponding amine and sulfone derivatives as shown in Schemes 14 and 15. Scheme 16 shows that the preparation of the nitrile derivative **16-2** can be achieved via a palladium catalyzed cyanation of the iodide **13-4**.

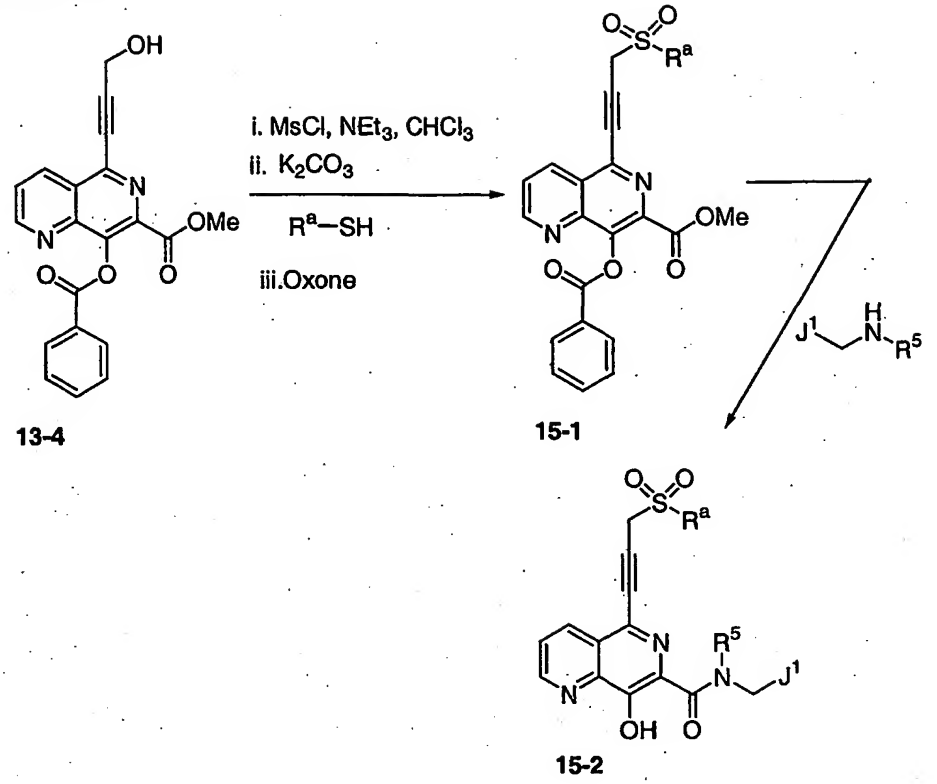
SCHEME 13



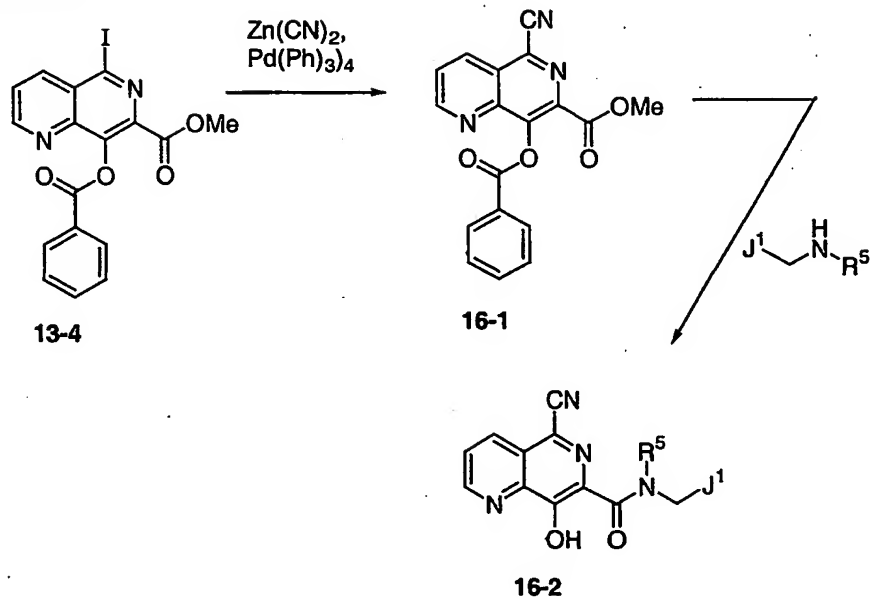
SCHEME 14


OH
OMe
i. MsCl, NEt3, CHCl3
ii. K2CO3
amine
CH2-AM
13-4
14-1
J1
H
N
R5
CH2-AM
AM = acyclyl-, cyclyl-, or heterocyclyl-amino
OH
14-2

SCHEME 15

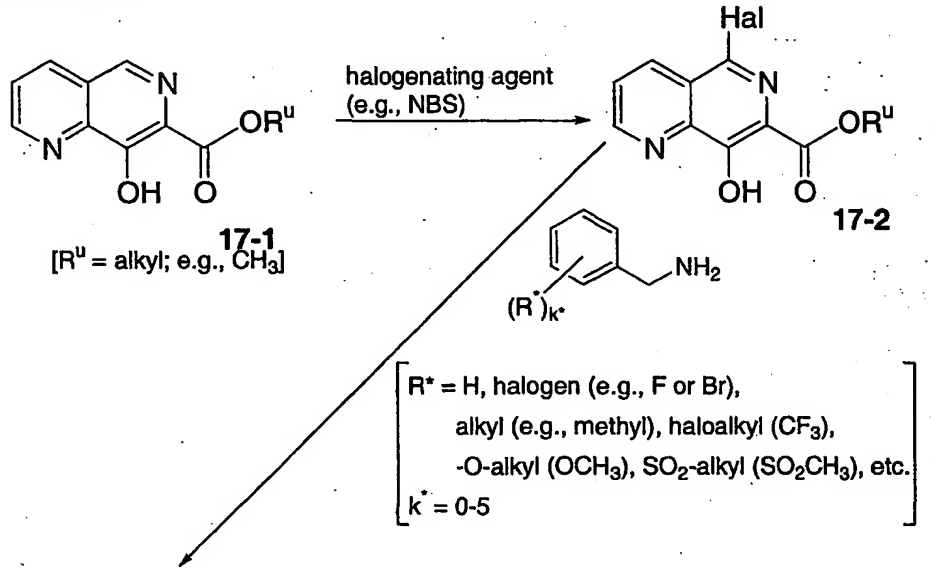


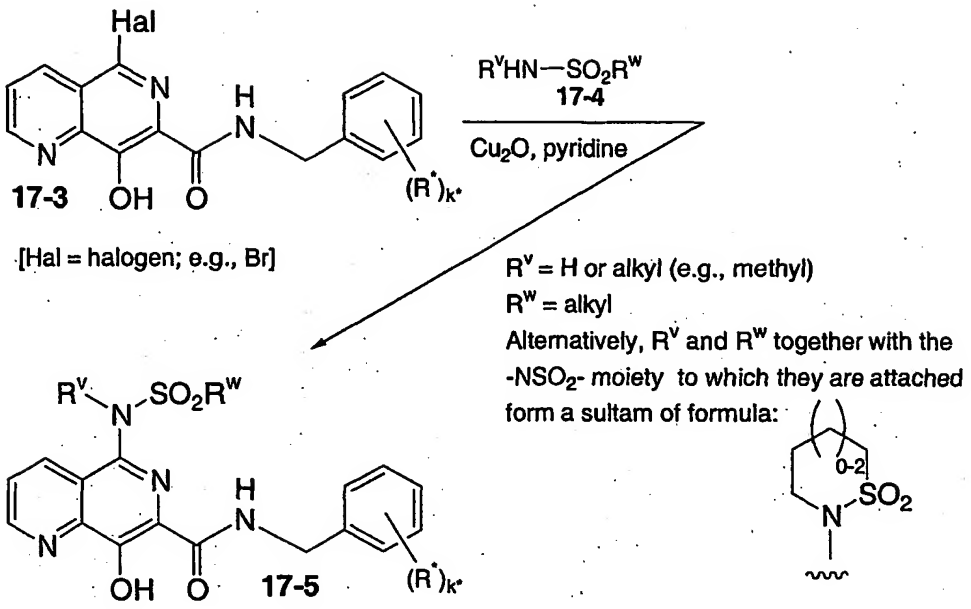
SCHEME 16



Preparation of compounds of the invention substituted with a sulfonamide can be prepared according to Scheme 17, which exemplifies the procedure for the naphthyridine core. The preparation includes halogenation of an alkyl 8-hydroxy-naphthyridine carboxylate (**17-1**) with a halogenation agent such as N-bromosuccinimide, coupling the halogenated ester (**17-2**) with substituted or unsubstituted benzylamine, and then condensing the 5-halo-8-hydroxy-naphthyridine carboxamide (**17-3**) with a sulfonamide (**17-4**) at elevated temperature (e.g., about 120 °C) in the presence of a copper promoter (e.g., copper(I) oxide) to afford the desired sulfonamidonaphthyridine product (**17-5**).

SCHEME 17



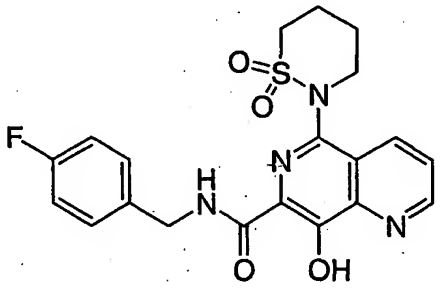


In the processes for preparing compounds of the present invention set forth in the foregoing schemes, functional groups in various moieties and substituents may be sensitive or reactive under the reaction conditions employed and/or in the presence of the reagents employed. Such sensitivity/reactivity can interfere with the progress of the desired reaction to reduce the yield of the desired product, or possibly even preclude its formation. Accordingly, it may be necessary or desirable to protect sensitive or reactive groups on any of the molecules concerned. Protection can be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973 and in T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known in the art. Alternatively the interfering group can be introduced into the molecule subsequent to the reaction step of concern. For example, if one or more of the substituents R^1, R^2, R^3, and R^4 in compound **1-1** can interfere with the coupling reaction between compounds **1-1** and **1-2** of Scheme 1, the substituent can be incorporated into the molecule in a post-coupling step to afford Compound I.

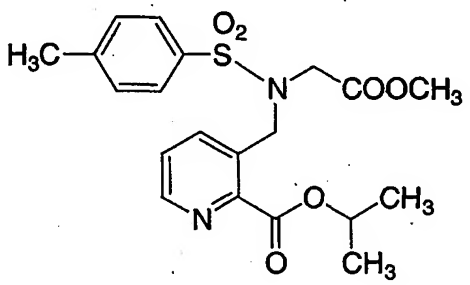
The following examples serve only to illustrate the invention and its practice. The examples are not to be construed as limitations on the scope or spirit of the invention.

EXAMPLE 1

5-(1,1-dioxido-1,2-thiazinan-2-yl)-*N*-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide



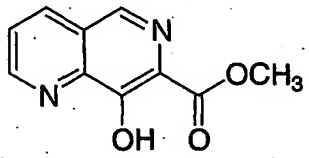
Step 1: Preparation of 3-{[Methoxycarbonylmethyl-(toluene-4-sulfonyl)-amino]-methyl}-pyridine-2-carboxylic acid isopropyl ester



Isopropyl 3-(hydroxymethyl)pyridine-2-carboxylate, (200 g, 1.02 mol; prepared as in P. Ornstein et. al. *J. Med. Chem.* 1989, 32, 827), methyl N-[(4-methylphenyl)sulfonyl]glycinate (249g, 1.02 mol), and triphenylphosphine (403g, 1.5 mol) were dissolved in dry THF (3000 mL) and cooled to 0°C under nitrogen. The diethylazodicarboxylate (DEAD) (267.6 g, 1.5 mol) was dissolved in dry THF (250 mL) and placed in a 500 mL addition funnel. The DEAD was added dropwise over 1 hour. The ice bath was removed and the reaction was allowed to warm slowly to room temperature. After 2 hours, the reaction was checked by HPLC and some glycinate remained. More starting reagents were added and the reaction was left to stir at room temperature. After 30 min, the reaction was checked again and a very

small amount of the glycinate remaining. The reaction mixture was concentrated down to a reddish-orange oil that was carried onto the next step.

Step 2: Preparation of methyl 8-hydroxy-1,6-naphthyridine-7-carboxylate

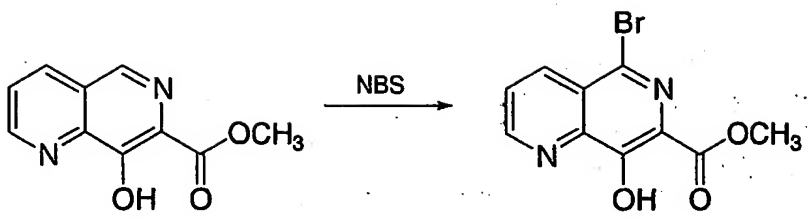


3-{[Methoxycarbonylmethyl-(toluene-4-sulfonyl)-amino]-methyl}-pyridine-2-carboxylic acid isopropyl ester (1.02 mol) was dissolved in dry methanol (4000ml) and cooled to 0°C under nitrogen. Then via addition funnel, sodium methoxide (137.8g, 2.5 mol) was added slowly to avoid any exotherm. The reaction was stirred at zero degrees, and checked by HPLC after 1.5 hours and was found to be completed. The solvent was removed *in vacuo* to obtain a reddish-orange oil, which was partitioned between water (1L) and ethyl acetate (1L). The organic layer was back extracted with saturated sodium bicarbonate solution. The pH of the aqueous layer was adjusted to 7, and the layer was maintained at this pH while extracting with methylene chloride. The organic layer was dried with Na_2SO_4, filtered, and the solvent was removed *in vacuo* to obtain a tan solid. The solid was dissolved in hot ethyl acetate, and the solution was filtered while hot to filter out any insoluble material. The product precipitated upon cooling. The precipitate was then filtered and dried in a vacuum oven. The filtrate was recrystallized by concentrating the filtrate and redissolving the resulting solid in a minimal amount of methylene chloride. Sufficient ethyl acetate was added to turn the solution slightly cloudy, after which the solution was boiled to reduce the volume, cooled, and the resulting crystals were filtered out and dried in a vacuum oven.

^1H NMR ($CDCl_3$, 500MHz) δ 11.794 (5H,s), 9.2 (1H,dd, *J*= 1.7 and 6.1Hz), 8.8 (1H,s), 8.3 (1H,dd, *J*= 1.5 and 9.7 Hz), 7.7 (1H, dd, *J*= 4.2 and 12.4 Hz), 4.1 (3H,s) ppm.

ES MS exact mass calculated for C10H8N2O3 204.1869 (MH+), found 205.1.

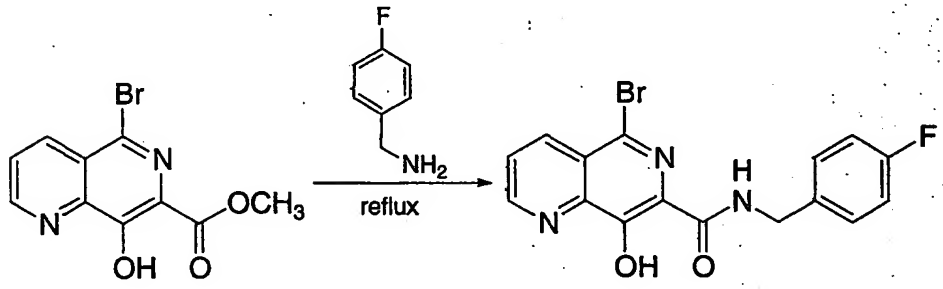
Step 3: Preparation of methyl 5-bromo-8-hydroxy-1,6-naphthyridine-7-carboxylate



To a solution of methyl 8-hydroxy-1,6-naphthyridine-7-carboxylate from Step 2 (5.0g, 24.49 mmol) in CH_2Cl_2 (100 mL) at room temperature was added N-bromosuccinimide (4.36g, 24.49 mmol). The reaction was stirred for 1hr. The solids were collected by filtration and dried in vacuo to afford the title compound as an off white solid.

FAB MS calcd for $C_{10}H_7Br\,N_2O_2$ 283 (MH^+), found 283.

Step 4: 5-bromo-N-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide



A slurry of the ester from Step 3 (0.50g, 0.177 mmol) and 4-fluorobenzylamine (0.243g, 1.94 mmol) in toluene (2 mL) were heated at reflux for 20 hrs. Upon cooling to room temperature, the resulting solids were collected by filtration and washed with methanol (3 mL) and then with diethyl ether (5 mL) to afford the title compound as a white solid.

^1H NMR ($CDCl_3$, 400MHz) δ 9.20 (1H, d, J=4.3 Hz), 8.56 (1H, d, J=8.4Hz), 8.17 (1H, m), 7.74 (1H, dd, J=8.4 and 4.3 Hz), 7.39 (2H, m), 7.07 (2H, t, J=8.6Hz), 4.67 (2H, d, J=6.2 Hz) ppm.

FAB MS calcd for $BrC_{16}H_{11}N_3O_2F$ 376 (MH^+), found 376.

Step 5: 5-(1,1-dioxido-1,2-thiazinan-2-yl)-*N*-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide

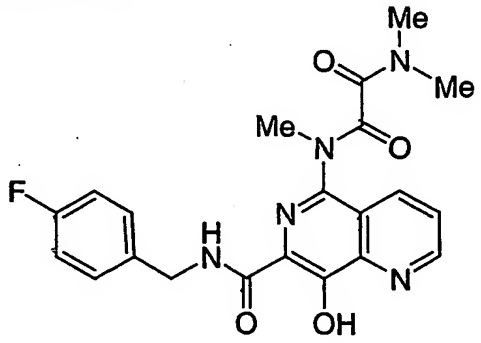
To a mixture of 1,4 butanesultam (prepared as in White et al, *J.Org Chem.* 1987, 52: 2162) (1.00 g, 7.40 mmol), 5-bromo-N-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide (3.06 g, 8.14 mmol), and Cu_2O (1.06 g, 7.40 mmol) under an atmosphere of argon was added pyridine (50 mL), and the suspension was stirred at reflux for 16 h. The reaction was allowed to cool to room temperature and filtered to remove the solids. The solids were washed with chloroform (500 mL). The resulting filtrate was evaporated to dryness and the residue was dissolved in chloroform (1 L) and vigorously stirred with a slurry of EDTA (4.0 g) in water (150 mL). After a period of 16 h, the chloroform extracts were dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by reverse phase HPLC. (Waters PrePak 500 cartridge C18, Gradient elution with Water : Acetonitrile 95:5 to 5:95 with 0.1% TFA at 75mL/min over 45mins). Lyophilization of the pure fractions afforded the title compound as an off-white solid.

^{1}H NMR (d_6 DMSO, 400MHz) δ 9.25 (1H, t, *J*=6.4Hz), 9.16 (1H, d, *J*=4.1Hz), 8.56 (1H, d, *J*=8.4Hz), 7.86 (1H, dd, *J*=8.4 and 4.1Hz), 7.41 (2H, dd, *J*=8.4 and 5.7Hz), 7.16 (2H, t, *J*=8.8Hz), 4.60 (2H, d, *J*=6.3Hz) 4.00-3.70(2H, m), 3.65-3.45 (2H, m), 2.35-2.10(3H, m), 1.70 (1H, m) ppm.

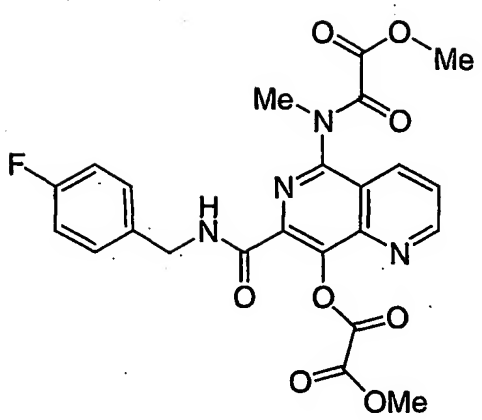
FAB MS calcd for $C_{20}H_{19}FN_4O_4S$ 431 (MH^+), found 431.

EXAMPLE 2

N-1-(7-{[(4-Fluorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)-N-1-,N-2-,N-2-trimethylethanediamide



Step 1: 7-{[(4-Fluorobenzyl)amino]carbonyl}-5-[[methoxy(oxo)acetyl]-(methyl)amino]-1,6-naphthyridin-8-yl methyl oxalate



Into a 50 mL flask fitted with a gas inlet and magnetic stir bar was placed 0.3 g (.92 mmol) N-(4-fluorobenzyl)-8-hydroxy-5-(methylamino)-1,6-naphthyridine-7-carboxamide, 0.961 mL (5.51 mmol) N,N-diisopropylethylamine and 20 mL CH_2Cl_2. The mixture was cooled to –78^{0}C and to it was added 0.338 mL (3.68 mmol) methyl chlorooxoacetate dropwise in 1 mL CH_2Cl_2. The reaction was then allowed to warm to ambient temperature and stirring was continued for 18 hrs, after which time the solvent was removed and the crude mixture was carried on without purification.

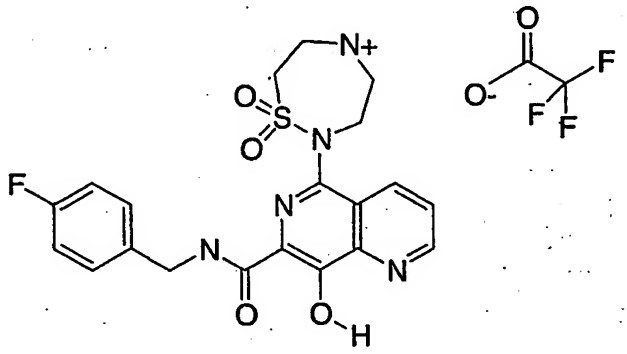
Step 2: N-1-(7-{[(4-Fluorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)-N-1-,N-2-,N-2-trimethylethanediamide hydrochloride

Into a 50 mL flask fitted with a gas inlet and magnetic stir bar was placed the crude reaction mixture from Step 1 and 20 mL methanol. The mixture was cooled to 0^{0}C with an ice bath and dimethylamine gas was bubbled into the reaction until saturated. The ice bath was removed and stirring was continued for an additional hour, after which time the solvent was removed in vacuo to give crude product which was purified by reverse phase HPLC on a C_{18} column using acetonitrile/water as eluent. The purified material was dissolved in 20 mL EtOAc, cooled to 0^{0}C and HCl gas bubbled through the solution briefly. The solvent was then removed in vacuo to give the title compound as a tan solid.
^{1}H NMR (400 MHz, DMSO, 135^{0}C) δ 9.16 (d, J = 4.3 Hz, 1H), 8.86 (s, 1H), 8.36 (s, 1H), 7.81 (dd, J = 4.3 Hz, 8.7 Hz, 1H), 7.43 (t, J = 5.9 Hz, 2H), 7.11 (t, J = 7.11 Hz, 2H), 4.61 (d, J = 6.7 Hz, 2H), 3.39 (s, 3H), 2.97 (s, 3H), 2.51 (s, 3H).

HRMS calc for $C_{21}H_{20}FN_5O_4$ (M+1): calc, 426.1572; found, 426.1570.

EXAMPLE 3

2-(7-{[(4-fluorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)-1,2,5-thiadiazepan-5-ium 1,1-dioxide trifluoroacetate



Step 1: Preparation of *tert*-butyl 2-[(vinylsulfonyl)amino]ethylcarbamate.

To a solution of N-Boc ethylenediamine (1.24g, 7.74mmol) in methylene chloride (35ml) at –10 C, was added triethylamine (2.37 ml, 17.0 mmol). 2-chloro-1-ethanesulfonyl chloride (0.809 mL, 7.74 mmol). After 4 hr at –10 C the cold bath was removed and the reaction was stirred for 12 hr at room temperature. The reaction was quenched by the addition of Na2CO3 (sat aq.) and extracted with methylene chloride. The organic extracts were dried (MgSO4) and the solvent evaporated in vacuo to afford the title compound as an oil which was used in the next step without further purification.

FAB MS calcd for $C_9H_{18}N_2O_4S$ 151 (MH^+-Boc), found 151.

^1H NMR ($CDCl_3$, 400MHz) δ 6.53 (1H, dd, *J*=9.9 and 16.5Hz), 6.24 (1H, d, *J*=16.5 Hz), 5.95 (1H, d, *J*=9.9 Hz), 5.09 (1H, s), 4.95 (1H, s), 3.28 (2H, m), 3.15 (2H, m), 1.45 (9H, s) ppm.

Step 2: Preparation of 2-[(vinylsulfonyl)amino]ethanaminium chloride.

A solution of *tert*-butyl 2-[(vinylsulfonyl)amino]ethylcarbamate (1.60 g, 6.39 mmol) in EtOAc (55ml) at 0 C, was saturated with HCl gas and then stirred for 1 hr. The solvent was evaporated in vacuo to afford the product as a viscous oil.

FAB MS calcd for $C_5H_{10}N_2O_2S$ 151 (MH^+), found 151.

^{1}H NMR (d_6DMSO, 400MHz) δ 8.06 (3H, s), 7.64 (1H, t, *J*=5.7Hz), 6.75 (1H, dd, *J*=9.9 and 16.5Hz), 6.08 (1H, d, *J*=16.5 Hz), 6.05 (1H, d, *J*=9.9 Hz), 3.15 (2H, m), 2.88 (2H, m) ppm.

Step 3: Preparation of 1,2,5-thiadiazepane 1,1-dioxide.

A solution of 2-[(vinylsulfonyl)amino]ethanaminium chloride (1.17 g, 6.24 mmol) in methanol (50 ml) at room temperature, was treated with triethylamine (0.87 mL, 6.24 mmol) and then stirred for 28 hr. Silica gel (10g) was added to the solution. The solvent was evaporated in vacuo and the remaining silica gel was applied to a column of silica gel and chromatographed eluting with 4% ammonium hydroxide in acetonitrile to afford the title compound as an oil.

FAB MS calcd for $C_5H_{10}N_2O_2S$ 151 (MH^+), found 151.

^{1}H NMR (d_6DMSO, 400MHz) δ 7.19 (1H, s), 3.26 (2H, m), 2.95-2.85 (6H, m), 2.88 (2H, m) and 2.60 (1H, m) ppm.

Step 4: Preparation of *tert*-butyl 1,2,5-thiadiazepane-5-carboxylate 1,1-dioxide.

To a solution of 1,2,5-thiadiazepane 1,1-dioxide 90.10 g, 0.67 mmol) in pyridine (1 mL) was added di-*tert*-butyldicarbonate 0.174g, 0.799 mmol). After 24 hr the reaction was quenched with NaHCO3 (sat aq.) and extracted into methylene chloride. The organic extracts were dried (MgSO4) and the solvent evaporated in vacuo. The residue was purified by chromatography (SiO2, EtOAc/CH2Cl2: 1:1) to afford the title compound as a white solid.

FAB MS calcd for $C_9H_{18}N_2O_4S$ 151 (MH^+-Boc), found 151.

^{1}H NMR (d_6DMSO, 400MHz) δ 7.46 (1H, m), 3.55 (2H, m), 3.48 (2H, m), 3.36-3.26 (2H, m), 3.06 (2H, m), 1.41 (9H, s) ppm.

Step 5: Preparation of *tert*-butyl 2-(7-{[(4-fluorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)-1,2,5-thiadiazepane-5-carboxylate 1,1-dioxide.

To a solution of 5-bromo-N-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide (0.188g, 0.50 mmol), *tert*-butyl 1,2,5-thiadiazepane-5-carboxylate 1,1-dioxide (0.12 g, 0.45 mmol) and Cu2O (0.071g, 0.50 mmol) in pyridine (3 mL) were heated at reflux for 16 hr. The reaction was filtered and the

solids washed with CHCl3 (100mL). The filtrate was stirred for 1 hr with disodium ethylenediamine tetraacetate (0.2 g in water 10mL) in the presence of air. The organic extracts were stirred for 1 hr with disodium ethylenediamine tetraacetate (0.2g in water 10mL) in the presence of air. The organic extracts were dried (MgSO4) and the solvent evaporated in vacuo. The residue was purified by preparative HPLC (Gilson semi preparative HPLC system and a YMC Combiprep Pro Column (50X20mm I.D., C18, S-5 um, 120A) eluting with 5 - 95% acetonitrile/water (0.1% TFA) at 15 ml/min) to afford the title compound after lyophilization.

^{1}H NMR (d_6DMSO, 400MHz) δ 9.28-9.18 (1.6H, m), 8.95(0.4H, m), 8.62 (0.6H, d, J=8.4Hz), 8.48 (1H, d, *J*=8.4Hz), 7.98-7.88 (1H, m), 7.54-7.42 (2H, m), 7.24-7.16 (2H, m), 4.75-4.45 (2H, m), 4.20-3.40 (8H, m), 1.43 (3.6H, s) 1.17 (5.4H, s) ppm.

FAB MS calcd for $C_{25}H_{28}FN_5O_6S$ 546 (MH^+), found 546.

Step 6: Preparation of 2-(7-{[(4-fluorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)-1,2,5-thiadiazepan-5-ium 1,1-dioxide trifluoroacetate.

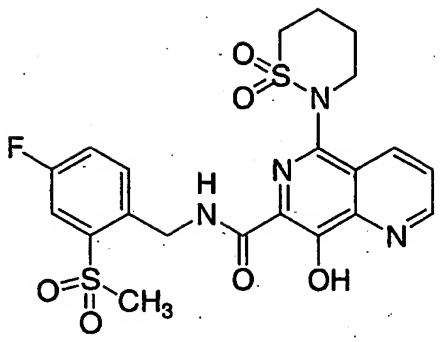
A solution of *tert*-butyl 2-(7-{[(4-fluorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)-1,2,5-thiadiazepane-5-carboxylate 1,1-dioxide (0.088g, 0.185 mmol) in methylene chloride (5 mL) was treated with trifluoroacetic acid (2 mL) at room temperature. After 6 hr the solvent was evaporated in vacuo and the residue purified by preparative HPLC (Gilson semi preparative HPLC system and a YMC Combiprep Pro Column (50X20mm I.D., C18, S-5 um, 120A) eluting with 5 - 95% acetonitrile/water (0.1% TFA) at 15 ml/min) to afford the title compound after lyophilization.

^{1}H NMR (d_6DMSO, 400MHz) δ 9.46 (1H, s), 9.24 (1H, d, *J*=4.1Hz), 8.59 (1H, d, *J*=8.4Hz), 7.95 (1H, dd, *J*=4.1 and 8.4Hz), 7.44 (2H, m), 7.19 (2H, m), 4.66 (2H, d, *J*=6.0Hz), 4.40-3.00 (8H, m), ppm.

FAB MS calcd for $C_{20}H_{20}FN_5O_4S$ 446 (MH^+), found 446.

EXAMPLE 4

Sodium 5-(1,1-dioxido-1,2-thiazinan-2-yl)-7-({[4-fluoro-2-(methylsulfonyl)benzyl]-amino}carbonyl)-1,6-naphthyridin-8-olate



Step 1: Preparation of 4-fluoro-2-(methylthio)benzonitrile.

2,4-difluorobenzonitrile (2.0 g, 14.38 mmol) and thiomethoxide (1.02 g, 14.38 mmol) were placed in an oven dried 100 mL round bottom flask fitted with a reflux condenser. Toluene (40 mL) was added and the reaction solution was put under an atmosphere of Argon. The reaction was heated to 90 deg C over 48 hours. The crude reaction was cooled and concentrated *in vacuo*. The residue was taken up in methylene chloride and extracted with water. The organic phase was dried (MgSO4), filtered and concentrated to afford a white solid. The solid was dissolved in a minimal amount of methylene chloride and purified on an ISCO column (110 g silica) with a gradient of 100% hexanes to 80% hexanes/20% ethylacetate over 15 min, then 20%EtOAc/80% Hexanes for 5 min. The collected fractions were evaporated *in vacuo* to afford the desired material in a 7.5:1 ratio 4-fluoro-2-(methylthio)benzonitrile: 2-fluoro-4-(methylthio)benzonitrile. The white solid was carried on to the next step without further purification.

^{1}H NMR ($CDCl_3$, 400MHz, major regioisomer) δ 7.56 (1H, dd, J = 5.58, 8.51 Hz), 6.95 (1H, dd, J = 2.38, 9.34 Hz), 6.88 (1H, dt, J = 2.38, 8.24 Hz), 2.54 (3H, s) ppm. EI HRMS exact mass calcd for C_8H_6FNS 167.0203, found 167.0205

Step 2: Preparation of 4-fluoro-2-(methylsulfonyl)benzonitrile.

4-fluoro-2-(methylthio)benzonitrile (1.59 g, 9.51 mmol, 7.5:1 mixture of regioisomers from Step 1) was dissolved in methylene chloride (50 mL) and 3-chloroperoxybenzoic acid (60% by weight, 4.6 g, 16 mmol) was added. The reaction was put under an atmosphere of Argon and stirred overnight at ambient temperature. The reaction was quenched with saturated aqueous sodium bicarbonate (2 x 100 mL). The organic phase still contained some 3-chloroperoxybenzoic acid by LCMS analysis so 1 mL DMSO was added and stirred for 1 hour. The organic phase was

then extracted again with saturated aqueous sodium bicarbonate (100 mL), dried (MgSO4), filtered and concentrated to afford the desired material as a 7:1 ratio of 4-fluoro-2-(methylsulfonyl)benzonitrile:2-fluoro-4-(methylsulfonyl)-benzonitrile. Selective crystallization from methanol, filtration and drying *in vacuo* afforded the desired 4-fluoro-2-(methylsulfonyl)benzonitrile as white crystals.

^{1}H NMR ($CDCl_3$, 400MHz, major regioisomer) δ 7.93 (1H, dd, J = 4.77, 8.51 Hz), 7.90 (1H, dd, J = 2.36, 7.70 Hz), 7.45 (1H, ddd, J = 2.56, 7.24, 8.47 Hz), 3.28 (3H, s) ppm.

EI HRMS exact mass calcd for $C_8H_6FNSO_2$ 199.0103, found 199.0103

Step 3: Preparation of 1-[4-fluoro-2-(methylsulfonyl)phenyl]methanaminium chloride.

4-fluoro-2-(methylsulfonyl)benzonitrile (5.6 g, 28.11 mmol) was added to a dry Parr bottle. Ethanol (50 mL) and conc HCl (10 mL) were added and the reaction solution put under an Argon atmosphere. 10% Pd/C (1 gram) was added and the reaction vessel placed on a Parr hydrogenation apparatus. The reaction was placed under an atmosphere of H2 (50 psi) and shaken overnight. After overnight the ratio of starting material to product was 50:50. The reaction was filtered through celite and concentrated slightly. Conc. HCl (10 mL) and 10% Pd/C (1 gram) were added and the reaction was again put under H2 (50 psi). The reaction was again shaken overnight. The crude reaction was filtered through celite and concentrated to afford the desired material as a white solid.

^{1}H NMR ($CDCl_3$, 400MHz) δ 7.86 (1H, dd, J = 2.74, 8.24 Hz), 7.74 (1H, dd, J = 5.03, 8.51 Hz), 7.57 (1H, dt, J = 2.75, 8.15 Hz), 4.45 (2H, s), 3.27 (3H, s) ppm.

MS calcd for $C_8H_{10}FNO_2S$ 203 (MH^+), found 204.

EI HRMS exact mass calcd for $C_8H_{10}FNO_2S$ 203.0410, found 203.0416

C,H,N calcd for $C_8H_{10}FNO_2S$ 1.1 HCl %C 39.49, %H 4.6, %N 5.76, found %C 39.50, %H 4.34, %N 5.56

Step 4: Preparation of methyl 5-bromo-8-{[(4-methylphenyl)sulfonyl]oxy}-1,6-naphthyridine-7-carboxylate.

To a slurry of methyl 5-bromo-8-hydroxy-1,6-naphthyridine-7-carboxylate (5.0 g, 17.66 mmol, prepared as in Example 113) in chloroform (20 mL) under nitrogen was added *N,N,N*-diisopropylethylamine (3.72 mL, 26.49 mmol). 4-

Methylbenzenesulfonyl chloride (4.04 g, 21.20 mmol) was added over 5 minutes and the reaction was heated to 40 degrees C and stirred one hour. The completed reaction was cooled to 25 degrees C and 1:1 methanol:water was added to precipitate the product which was filtered, washed with more 1:1 methanol:water and dried *in vacuo*. This afforded the desired product as a solid.

^{1}H NMR (*d*-DMSO, 400MHz) δ 9.03 (1H, dd, *J* = 4.4, 1 Hz), 8.64 (1H, dd, *J* = 8.8, 1.0 Hz), 7.92 (1H, dd, *J* = 8.8, 4.4 Hz), 7.70 (2H, d, *J* = 8.0), 7.40 (2H, d, *J* = 8.0 Hz), 3.76 (3H, m), 2.42 (3H, m) ppm.

FAB HRMS exact mass calcd for $C_{17}H_{13}BrN_2O_5S$ 436.9802 (MH^+), found 436.9807

Step 5: Preparation of methyl 5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-{[(4-methylphenyl)sulfonyl]oxy}-1,6-naphthyridine-7-carboxylate.

To a slurry of methyl 5-bromo-8-{[(4-methylphenyl)sulfonyl]oxy}-1,6-naphthyridine-7-carboxylate (7.55 g, 17.27 mmol) in degassed DMF (20 mL) in a pressure tube was added 1,2-thiazinane-1,1-dioxide (2.8 g, 20.7 mmol, prepared as in White et al, *J.Org Chem.* 1987, 52: 2162) followed by 2,2'-bipyridine (3.24 g, 20.7 mmol) and copper (I) oxide powder (2.96 g, 20.7 mmol). The pressure tube was closed and heated to 118 degrees C overnight. Celite (0.5 g) was added to the resulting slurry and this was filtered through a plug of DMF wetted celite. The solids were washed with more DMF (10 mL) and the filtrate transferred to a large Erlenmeyer flask (1L) fitted with a 2 inch stirring bar. The volume was brought up to 200 mL with chloroform and a solution of ethylenediaminetetraacetic acid monohydrate (13.3 g, 35.7 mmol) in 140 mL of water was added. The biphasic mixture was vigorously stirred, open to the air, for 3 hours. The organic phase was separated and retreated with another solution of ethylenediaminetetraacetic acid monohydrate (13.3 g, 35.7 mmol) in 140 mL of water overnight (16 hrs). The organic was separated and washed with water and dried over Na2SO4, filtered, and reduced to a small volume *in vacuo*. The product solidified during solvent reduction. The solid was broken up and dried to afford the desired product.

LCMS calcd for $C_{21}H_{21}N_3O_7S_2$ 492.082 (MH^+), found 492.51

Step 6: Preparation of methyl 5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxylate.

To a solution of methyl 5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-{[(4-methylphenyl)sulfonyl]oxy}-1,6-naphthyridine-7-carboxylate (6.0 g, 12.2 mmol) in DMF (50 mL) under nitrogen at zero degrees C was added sodium methoxide (49.40 mL, 24.70 mmol, 0.5 M in Methanol). The cold solution was allowed to stir for one hour. Acetic acid (1.64 mL, 27.4 mmol) was added followed by water to precipitate the product. The mixture was allowed to stand for one hour. The crude reaction was filtered and the solids were washed with 1:1 methanol:water and dried *in vacuo* to afford the desired product.

^{1}H NMR (*d*-DMSO, 400MHz) δ 9.20 (1H, d, *J* = 4.0 Hz), 8.61 (1H, d, *J* = 8.4 Hz), 7.91 (1H, dd, *J* = 8.4, 4.0 Hz), 3.96 (3H, m), 3.87 (1H, bs), 3.79 (1H, bs), 3.32 (2H, m), 2.27 (3H, m), 1.66 (1H, m) ppm.

FAB HRMS exact mass calcd for $C_{14}H_{15}N_3O_5S$ 338.0805 (MH^+), found 338.0793

C, H, N calculated for $C_{14}H_{15}N_3O_5S \cdot 0.40\ H_2O$ %C 48.80, %H 4.62, %N 12.20, found %C 48.79, %H 4.35, %N 12.15.

Step 7: Preparation of 5-(1,1-dioxido-1,2-thiazinan-2-yl)-N-[4-fluoro-2-(methylsulfonyl)benzyl]-8-hydroxy-1,6-naphthyridine-7-carboxamide.

To a slurry of methyl 5-(1,1-dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxylate (2.11 g, 6.26 mmol) in ethanol (30 mL) in a pressure flask was added 1-[4-fluoro-2-(methylsulfonyl)phenyl]methanaminium chloride followed by *N,N,N*-diisopropylethylamine (2.17 mL, 12.52 mmol). The pressure flask was purged with nitrogen and closed. The reaction was heated to 80 degrees C for 16 hours. The reaction containing residual solids was cooled and determined to be incomplete by LCMS analysis. Added degassed DMF (10 mL) to solubilize the remaining solids, resealed the pressure tube and reheated to 80 degrees C overnight. The reaction was cooled, transferred to a round bottom flask and reduced to a small volume *in vacuo*. The residue was partitioned between methylene chloride and saturated aqueous sodium bicarbonate. The organic layer was washed with water, dried over Na2SO4, filtered and reduced to a small volume *in vacuo*. The residue was crystallized via the addition of 5 mL of methanol. The crystals were filtered and dried *in vacuo* to afford the title compound.

^{1}H NMR (*d*-DMSO, 400MHz) δ 13.41 (1H, s), 9.19 (2H, d, *J* = 4.0 Hz), 8.60 (1H, d, *J* = 8.4 Hz), 7.89 (1H, dd, *J* = 8.4, 4.0 Hz), 7.79-7.71 (2H, m), 7.64 (1H, dd, *J* = 8.4,

2.4 Hz), 4.98 (2H, d, J = 3.6 Hz), 3.84 (2H, m), 3.48 (5H, m), 2.29 (3H, m), 1.69 (1H, bs) ppm.

APCI HRMS exact mass calcd for $C_{21}H_{21}FN_4O_6S_2$ 509.0960 (MH^+), found 509.0936

C, H, N calculated for $C_{21}H_{21}FN_4O_6S_2 \cdot 0.15\ H2O$ %C 49.33, %H 4.20, %N 10.96, found %C 49.37, %H 4.08, %N 10.85.

Step 8: Preparation of sodium 5-(1,1-dioxido-1,2-thiazinan-2-yl)-7-({[4-fluoro-2-(methylsulfonyl)benzyl]amino}carbonyl)-1,6-naphthyridin-8-olate.

To a slurry of the free base (0.25 g, 0.5 mmol) from step 7 in acetone (10 mL) was added methanol (2 mL) and 1 N aqueous NaOH (0.49 mL, 0.49 mmol). The yellow solution was reduced to a small volume and the residue was crystallized from methanol. The crystals were filtered and dried *in vacuo* to afford the sodium salt form of the title compound.

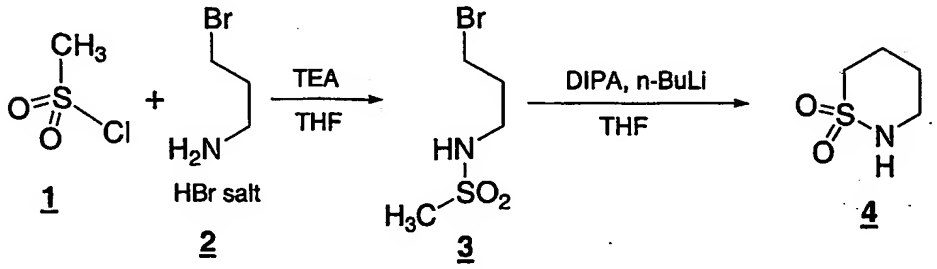
^{1}H NMR (*d*-DMSO, 400MHz) δ 12.41 (1H, m), 8.79 (1H, dd, J = 4.0, 1.6 Hz), 8.26 (1H, dd, J = 8.4, 1.6 Hz), 7.71-7.57 (3H, m), 7.54 (1H, dd, J = 8.4, 4.0 Hz), 4.90 (2H, d, J = 6.0 Hz), 3.88-3.77 (2H, m), 3.48 (4H, m), 3.20 (1H, m), 2.50 (1H, m), 2.22 (2H, m), 1.49 (1H, m) ppm.

APCI HRMS exact mass calcd for $C_{21}H_{20}FN_4O_6S_2$ 531.0779 (M+Na), found 531.0811

C, H, N calculated for $C_{21}H_{20}FN_4NaO_6S_2 \cdot 0.85\ H2O$ %C 46.21, %H 4.01, %N 10.27, found %C 46.19, %H 3.68, %N 10.02.

EXAMPLE 5

Preparation of 1,4-Butanesultam



	Weight	FW	Moles	Equiv.	Density	Volume
MsCl (1)	2.36 Kg	114.55	20.6	1.03	1.480	1.59 L
3-bromopropyl-amine (2) HBr salt	4.40 Kg	220	20.0	1.00		
TEA	4.07 Kg	101.19	40.2	2.01	0.726	5.60 L
THF					43 + 4 + 8 = 55 L	
DIPA	481 g	101.19	4.75	0.25	0.722	666 mL
1,10-Phenanthroline	4.11 g	180.21				
n-BuLi, 1.6 M in hexane						

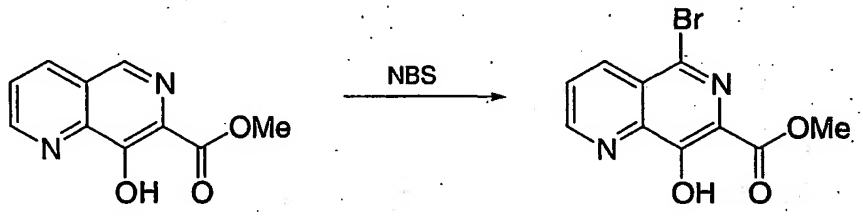
The 3-bromopropylamine-HBr salt (2) and THF (43 L) were placed in a 72 L round-bottomed-flask under N_2 and the resulting slurry was cooled to 0 °C. Two dropping funnels were fitted to the flask. One was charged with the TEA and the other with a solution of the MsCl (1) and THF (4 L). The contents of the addition funnels were added at roughly the same rate (the TEA was added slightly faster than the MsCl) while maintaining an internal reaction temperature below 10 °C. The addition required 2 h. The resulting white suspension was warmed to 23 °C and aged for 1 h. The suspended solids (a mixture of TEA-HBr and TEA-HCl) were removed by filtration through a dry frit. The cake was washed with THF (8 L). The combined filtrate and cake-rinse, a THF solution of 3, was collected in a 100 L round-bottomed-flask under N_2. To the solution of 3 was added the 1,10-phenanthroline and the DIPA and the resulting solution was cooled to -30 °C. The *n*-BuLi was added over about 4 h maintaining the internal temperature below -20 °C. After 1.25 eq of the *n*-BuLi was added the reaction mixture became deep brown and the color remained as the addition was completed. The reaction mixture was warmed to 0 °C over 3 h. A small aliquot was removed, and partitioned between saturated NH_4Cl and EtOAc. The EtOAc was evaporated and the residue examined by ^1H NMR to confirm consumption of 3 and conversion to 4. To the reaction mixture at 0 °C was added saturated aqueous NH_4Cl (12 L, the first 1L slowly, a heat kick to 6 °C was observed) and then brine (12 L). The phases were partitioned and the aqueous phase was extracted with EtOAc (20 L). The organic phases were combined, washed with brine (4 L) and then concentrated under vacuum to about 12 L. The solvent was switched to EtOAc (20 L used)

maintaining a volume of 12 L. After the solvent switch, a yellow slurry resulted. *n*-Heptane (20 L) was added with stirring and the slurry was cooled to 5 °C. After a 1h age the solids were collected on a frit and rinsed with cold (5 °C) 3:5 EtOAc/*n*-heptane. The wet cake was dried for 24 h under a stream of dry N_2 to provide 1.44 Kg (53% from 2) of sultam 4 as a crystalline yellow solid.

EXAMPLE 6

Preparation of 5-(1,1-dioxido-1,2-thiazinan-2-yl)-*N*-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide from methyl 5-bromo-8-hydroxy-1,6-naphthyridine-7-carboxylate

Step 1: 5-Bromo-8-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester



5
[204.19]

6
[283.63]

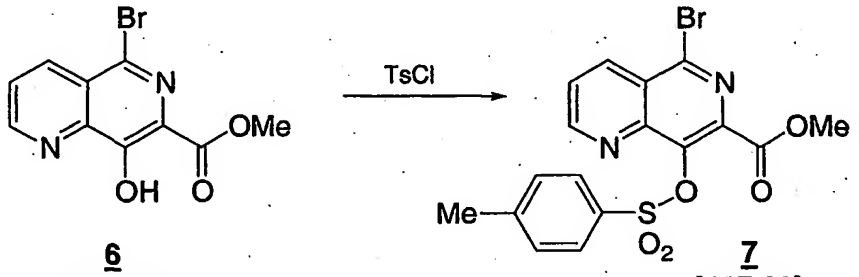
N-bromosuccinimide (7.83 g, 44.0 mmol) was added to a solution of 8-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester (5, 8.17 g, 40.0 mmol) in chloroform (32 mL) over 20 min maintaining the temperature at 20-50 °C and the mixture was aged for 30 min at 50 °C. The mixture became a thick, stirrable slurry and HPLC analysis indicated <2% starting material remaining. The mixture was cooled to 30 °C over 15 min. MeOH (64 mL) was added over 30 min then a 1:1 mixture of MeOH-water (64 mL) was added over 30 min. The mixture was cooled to –40 °C over 30 min and aged at –40 °C for 30 min. The cold mixture was filtered and the solid was washed with 1:1 MeOH:water (100 mL) at 10-20 °C. The off white crystalline solid was dried under a stream of nitrogen to provide 10.48 g (93% yield) of 5-bromo-8-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester (6).

HPLC retention times: 5 = 2.2 min, 6 = 6.0 min, HPLC conditions: 150 x 4.6 mm ACE 3 C18 column, isocratic elution with 30% MeCN in 0.025% aq H_3PO_4 at 1 mL/min, 25 °C with detection at 254 nm;

HPLC retention times: 5 = 1.8 min, 6 = 3.1 min, HPLC conditions: 150 × 4.6 mm ACE 3 C18 column, isocratic elution with 46% MeCN in 0.025% aq H_3PO_4 at 1 mL/min, 25 °C with detection at 254 nm.

^{13}C NMR of 6 ($CDCl_3$, 100 MHz): 169.7, 156.3, 154.5, 143.9, 137.1, 132.4, 128.0, 126.1, 124.2, 53.4.

Step 2: 5-Bromo-8-(4-toluenesulfonyloxy)-1,6-naphthyridin-7-carboxylic acid methyl ester



6
[283.63]

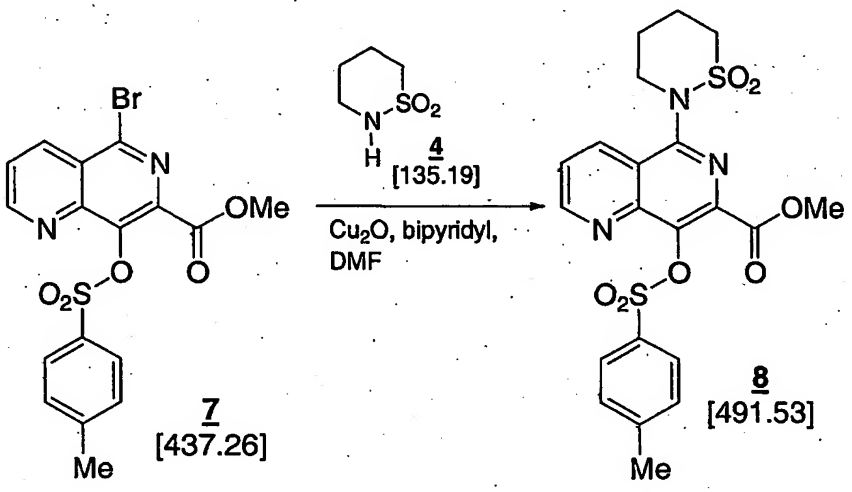
7
[437.26]

Triethylamine (0.759 g, 7.50 mmol) was added to a suspension of 5-bromo-8-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester (6, 1.415 g, 5.000 mmol) in chloroform (5 mL) over 5 min maintaining the temperature at 20-50 °C to give a yellow suspension. *p*-Toluenesulfonyl chloride (1.15 g, 6.00 mmol) was added over 5 min maintaining the temperature at 20-40 °C to give a yellow solution. The mixture was aged at 40 °C for 2 h during which a crystalline solid precipitated out of the mixture and the color faded (HPLC analysis indicated <0.5% starting material remaining). The mixture was cooled to 20 °C over 15 min. MeOH (10 mL) was added over 30 min then a 1:1 mixture of MeOH:water (10 mL) was added over 30 min. The mixture was cooled to –40 °C over 30 min and aged at –40 °C for 30 min. The cold mixture was filtered and the solid was washed with 1:1 MeOH:water (10 mL), MeOH (5 mL), MTBE (10 mL) and hexanes (10 mL) all at 10-20 °C. The off-white crystalline solid was dried under a stream of nitrogen to provide 2.112 g (97% yield) of 5-bromo-8-(*p*-toluenesulfonyloxy)-1,6-naphthyridine-7-carboxylic acid methyl ester (7).

HPLC retention times: 6 = 3.1 min, 7 = 12.4 min, HPLC conditions: 150 × 4.6 mm ACE 3 C18 column, isocratic elution with 46% MeCN in 0.025% aq H_3PO_4 at 1 mL/min, 25 °C with detection at 254 nm.

^{13}C NMR of 7 (d6-DMSO, 100 MHz): 163.2, 157.0, 146.5, 145.8, 141.9, 141.3, 139.2, 137.2, 132.3, 130.4, 129.0, 127.6, 127.1, 53.3, 21.7.

Step 3: 5-(1,1-Dioxido-1,2-thiazinan-2-yl)-8-(4-toluenesulfonyloxy)-1,6-naphthyridine-7-carboxylic acid methyl ester.



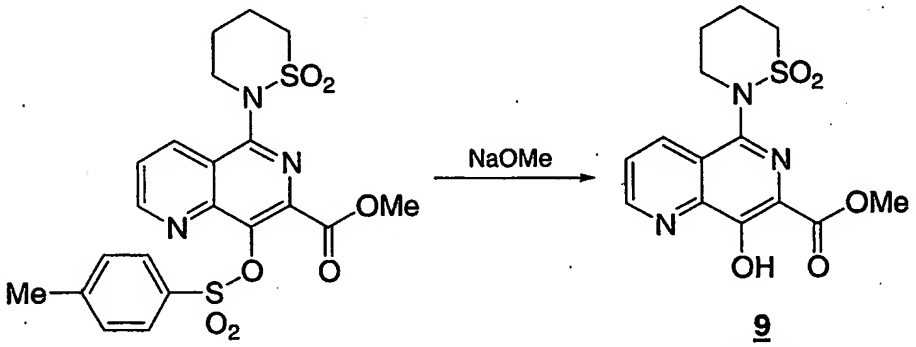
A mixture of 5-bromo-8-(*p*-toluenesulfonyloxy)-1,6-naphthyridine-7-carboxylic acid methyl ester (7, 2.186 g, 5.000 mmol), 1,4-butane sultam (4, 811 mg, 6.00 mmol), copper (I) oxide (858 mg, 6.00 mmol, <5 micron), 2,2'-bipyridyl (937 mg, 6.00 mmol) and DMF (10 mL) was degassed by stirring under a stream of nitrogen for 1 min and heated to 120 °C for 4 h. The brown suspension became a dark red solution with a small amount of undissolved copper (I) oxide remaining (HPLC analysis indicated <0.5% starting material remaining). The mixture was diluted with chloroform (10 mL), Solkaflok (200 mg) was added and the resulting mixture was filtered through a plug of Solkaflok. The plug was washed with chloroform (10 mL) and the combined filtrates were stirred vigorously with a solution of EDTA disodium salt dihydrate (3.8 g, 10.2 mmol) in water (40 mL) while air was slowly bubbled in for 40 min. The upper aqueous phase became turquoise while the lower organic phase became yellow. The organic phase was washed with a solution of EDTA disodium salt (1.9 g, 5.1 mmol) in water (30 mL) and a solution of sodium bisulfate monohydrate (0.87g, 6.3 mmol) in water (30 mL). Each of the above three aqueous phases was back extracted sequentially with one portion of chloroform (15 mL). The organic phases were dried over sodium sulfate and filtered. The dried

organic extracts were concentrated and solvent switched to a final volume of 15 mL MeOH using a total of 30 mL MeOH for the switch at atmospheric pressure. Product crystallized during the solvent switch. The resulting slurry was cooled to 0 °C over 30 min and aged at 0 °C for 30 min. The slurry was filtered cold and the solid was washed with MeOH (15 mL). The off white solid was dried under a stream of nitrogen to provide 1.910 g (78%) of 5-(*N*-1,4-butanesultam)-8-(*p*-toluenesulfonyloxy)-1,6-naphthyridine-7-carboxylic acid methyl ester (**8**).

HPLC retention times: **7** = 12.4 min, **8** = 10.3 min, DMF = 1.3 min, Bipy = 1.5 min, HPLC conditions: 150 × 4.6 mm ACE 3 C18 column, isocratic elution with 46% MeCN in 0.025% aq H_3PO_4 at 1 mL/min, 25 °C with detection at 254 nm.

^{13}C NMR of **8** ($CDCl_3$, 100 MHz): 164.2, 155.3, 151.9, 146.7, 145.4, 141.2, 137.8, 135.3, 133.6, 129.6, 128.9, 125.4, 124.3, 53.4, 52.9, 48.7, 24.2, 22.0, 21.7.

Step 4: 5-(1,1-Dioxido-1,2-thiazinan-2-yl)-8-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester.



8
[491.53]

9
[337.35]

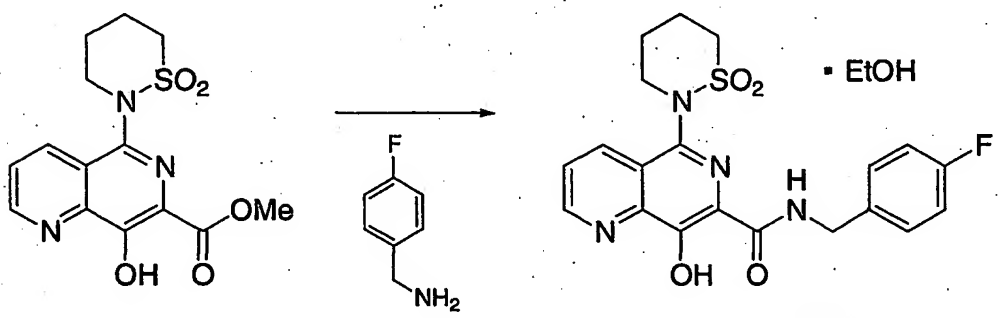
5-(*N*-1,4-butanesultam)-8-(*p*-toluenesulfonyloxy)-1,6-naphthyridine-7-carboxylic acid methyl ester (**8**, 1.597 g, 3.250 mmol) was dissolved in DMF (3.25 mL) at 40 °C and transferred to a solution of 0.5M NaOMe in MeOH (16.25 mL, 8.125 mmol) over ca 1-2 min at 20-25 °C. The resulting yellow homogenous mixture was heated to 50 °C and aged for 5 min (HPLC analysis indicated <0.5% starting material remaining). Mixture was cooled to 25 °C over 15 min and aged at 25 °C for 15 min during which a yellow crystalline precipitate was deposited. Acetic acid (390 mg, 6.50 mmol) was added over 1 min (yellow color faded) then water (32.5 mL) was

added over 15 min at 25 °C. The slurry was aged for 30 min 25 °C and filtered. The filter cake was washed with 1:1 MeOH:water (32.5 mL) and then with 1:1 MTBE:hexanes (8 mL). The filter cake was dried under a stream of nitrogen to provide 1.064 g (97%) of 5-(*N*-1,4-butanesultam)-8-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester (**9**) as an off white crystalline solid.

HPLC retention times: **8** = 10.3 min, **9** = 2.9 min, HPLC conditions: 150 × 4.6 mm ACE 3 C18 column, isocratic elution with 46% MeCN in 0.025% aq H_3PO_4 at 1 mL/min, 25 °C with detection at 254 nm.

^{13}C NMR of **9** (d6-DMSO, 100 MHz): 167.8, 154.4, 153.5, 143.9, 143.7, 135.2, 125.9, 125.2, 124.4, 53.2, 53.1, 49.1, 24.4, 21.9.

Step 5: 5-(1,1-Dioxido-1,2-thiazinan-2-yl)-*N*-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide, monoethanolate.



9 [337.35]

10 [125.15]

11• EtOH [476.52]

A suspension of 5-(*N*-1,4-butanesultam)-8-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester (**9**, 1.012 g, 3.00 mmol) and 4-fluorobenzylamine (**10**, 1.314 g, 10.5 mmol) in EtOH (9.0 mL) was heated to 75-77 °C for 2 h during which the mixture became a yellow homogeneous solution (HPLC analysis indicated <0.5% starting material remaining). Acetic acid (0.630 mg, 10.5 mmol) was added over 1 min (yellow color faded) then water (9.0 mL) was added over 10 min at 75 °C. An off white crystalline solid began to precipitate near the end of addition of the water. The slurry was cooled to 0 °C over 30 min then aged for 30 min at 0 °C and filtered. The filter cake was washed with 5% HOAc in 1:1 EtOH:water (5 mL) then with 1:1 EtOH:water (10 mL) and then with EtOH (5 mL). The filter cake was dried under a stream of nitrogen to provide 1.343 g (94%) of the monoethanolate of 5-(*N*-1,4-

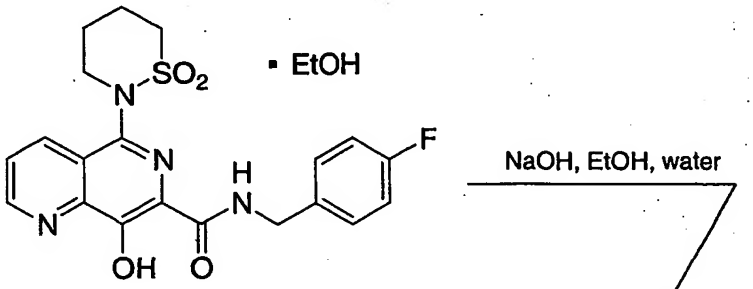
butanesultam)-*N*-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide (11) as an off white crystalline solid.

HPLC retention times: 9 = 2.9 min, 11 = 6.7 min, 10 = 1.4 min, impurity present in 10 = 4.3 min, HPLC conditions: 150 × 4.6 mm ACE 3 C18 column, isocratic elution with 46% MeCN in 0.025% aq H_3PO_4 at 1 mL/min, 25 °C with detection at 254 nm;

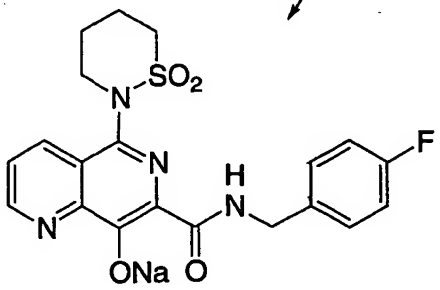
HPLC retention time: 9 = 10.9 min, HPLC conditions: 150 × 4.6 mm ACE 3 C18 column, isocratic elution with 24% MeCN in 0.025% aq H_3PO_4 at 1 mL/min, 25 °C with detection at 254 nm.

^{1}H NMR (d6-DMSO, 400 MHz): 9.25 (t, J=6.4, 1H), 9.16 (d, J=8.4, 1H), 8.56 (d, J=8.4, 1H), 7.86 (dd, J=8.4, 4.1, 1H), 7.41 (dd, J=8.4, 5.7, 2H), 7.16, t, J=8.8, 2H), 4.60 (d, 6.3, 2H), 4.00-3.70 (m, 2H), 3.65-3.45 (m, 2H), 2.35-2.10 (m, 3H), 1.7 (m, 1H).

Step 6: Sodium salt of 5-(1,1-Dioxido-1,2-thiazinan-2-yl)-*N*-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide



Ethanolate of 11
[476.52]



Na salt of 11
[452.44]

5-(*N*-1,4-Butanesultam)-*N*-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide (11) monoethanolate (1.207 g, 2.533 mmol) was dissolved in a mixture of EtOH (24 mL) and water (11 mL) by heating to 78 °C for 1 h. A solution of 5M aq NaOH (0.608 mL, 3.04 mmol) was added over 15 min at 78 °C. A yellow crystalline precipitate was deposited. The mixture was aged at 78 °C for 20 min, then cooled to 20 °C over 30 min and aged for 30 min at 20 °C. The slurry was filtered and the filter cake was washed with 2:1 EtOH:water (5 mL) and EtOH (15 mL). The filter cake was dried under a stream of nitrogen to provide 1.088 g (95%) of 5-(*N*-1,4-butanesultam)-*N*-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide sodium salt (11 sodium salt) as a yellow crystalline solid.

The Na salt was analyzed by differential scanning calorimetry at a heating rate of 10°C/min in an open cup under flowing nitrogen and was found to have a DSC curve exhibiting an endotherm with a peak temperature of about 348°C and an associated heat of fusion of about 45 J/gm followed by an exotherm with a peak temperature of about 352°C and an associated heat of fusion of about 45 J/gm.

The XRPD pattern of the Na salt was generated on a Philips Analytical X-ray powder diffraction (XRPD) instrument with XRG 3100 generator using a continuous scan from 2 to 40 degrees 2 theta over about 126 minutes. The resulting XRPD pattern was analyzed using Philips X'Pert Graphics and Identify software. Copper K-Alpha 1 radiation was used as the source. The experiment was run under ambient conditions. The XRPD pattern was found to have characteristic diffraction peaks corresponding to d-spacings of 12.63, 5.94, 5.05 , 4.94, 4.81, 4.61, 4.54, 4.34, 3.88, 3.73, 3.49, 3.45, 3.22, 3.15, 3.12, and 2.86 angstroms.

The Na salt has been jet-milled to provide crystals with a mean particle size of about 3 to 5 microns (v. about 20 to 25 microns for unmilled material) for use in orally administered formulations. The jet-milled salt has exhibited improved oral bioavailability over the unmilled salt.

EXAMPLE 7

Oral Composition

As a specific embodiment of an oral composition of a compound of this invention, 50 mg of compound of Example 1 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule.

EXAMPLE 8

HIV Integrase Assay: Strand Transfer Catalyzed by Recombinant Integrase

Assays for the strand transfer activity of integrase were conducted in accordance with Wolfe, A.L. et al., *J. Virol.* 1996, 70: 1424-1432, for recombinant integrase, except that: (i) the assays used preassembled integrase strand transfer complexes; (ii) the strand transfer reaction was performed in the presence of inhibitor in 2.5 mM $MgCl_2$ using 0.5 to 5 nM of a 3' FITC labeled target DNA substrate

5'		TGA	CCA	AGG	GCT	AAT	TCA	CT	fitc 3'
3'	fitc	ACT	GGT	TCC	CGA	TTA	AGT	GA	5';

and (iii) strand transfer products were detected using an alkaline phosphatase conjugated anti-FITC antibody and a chemiluminescent alkaline phosphatase substrate. Representative compounds tested in the integrase assay demonstrated IC_{50}'s of less than about 100 micromolar.

Further description on conducting the assay using preassembled complexes is found in Hazuda et al., *J. Virol.* 1997, 71: 7005-7011; Hazuda et al., *Drug Design and Discovery* 1997, 15: 17-24; and Hazuda et al., *Science* 2000, 287: 646-650.

EXAMPLE 9

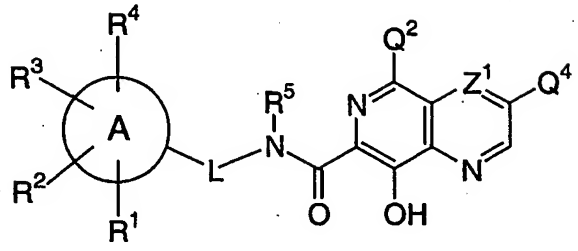
Assay for inhibition of HIV replication

Assays for the inhibition of acute HIV infection of T-lymphoid cells were conducted in accordance with Vacca, J.P. et al., (1994), Proc. Natl. Acad. Sci. USA 91, 4096. Representative compounds tested in the present assay demonstrated IC_{95}'s of less than about 20 micromolar.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, the practice of the invention encompasses all of the usual variations, adaptations and/or modifications that come within the scope of the following claims.

WHAT IS CLAIMED IS:

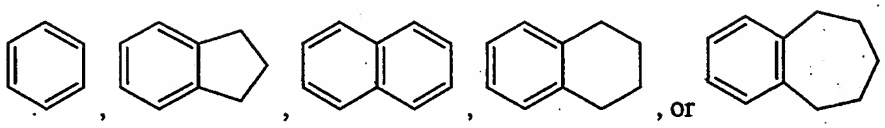
1. A compound of Formula (I):



(II),

wherein

A is



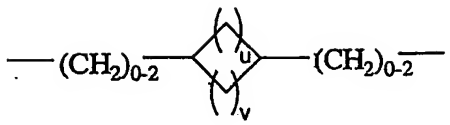
L is

(i) a single bond;

(ii) $-(CH_2)_{1-3}-$, which is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, -OH, $-C_{1-4}$ alkyl, $-O-C_{1-4}$ alkyl, $-CO_2CH_3$, $-CO_2CH_2$-phenyl, phenyl, benzyl, $-(CH_2)_{1-2}OH$, -CH(OH)-phenyl, and $-CH(NH_2)$-phenyl;

(iii) $-(CH_2)_{0-1}-CH=CH-(CH_2)-$, which is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, -OH, $-C_{1-4}$ alkyl, and $-O-C_{1-4}$ alkyl;

(iv)



, wherein u and v are each integers having a value of from 0 to 4, provided that the sum of u + v is 1, 2, 3 or 4; or

(v) a heteroatom-containing chain which is $-N(R^a)-(CH_2)_{1-2}-$, $-CH_2-OC(=O)-CH_2-$, or $-CH_2-C(=O)O-CH_2-$;

Z^1 is N or C-Q^3;

Q^2 and Q^3 are as defined in (i) or (ii) as follows:

(i) Q^2 is

(1) -H,
(2) $-C_{1-4}$ alkyl,
(3) $-C_{1-4}$ fluoroalkyl,
(4) $-O-C_{1-4}$ alkyl,
(5) $-O-C_{1-4}$ fluoroalkyl,
(6) halo,
(7) -CN,
(8) $-C_{1-4}$ alkyl-OR^a,
(9) $-(CH_2)_{0-2}C(=O)R^a$,
(10) $-(CH_2)_{0-2}CO_2R^a$,
(11) $-(CH_2)_{0-2}SR^a$,
(12) $-N(R^a)_2$,
(13) $-C_{1-4}$ alkyl $-N(R^a)_2$,
(14) $-(CH_2)_{0-2}C(=O)N(R^a)_2$,
(15) $-G-C_{1-6}$ alkyl-$C(=O)N(R^a)_2$, wherein G is O, S, $N(R^a)$, or $N(SO_2R^a)$,
(16) $-N(R^a)-C(R^a)=O$,
(17) $-(CH_2)_{1-3}-N(R^a)-C(R^a)=O$,
(18) $-C(=O)-N(R^a)-(CH_2)_{1-3}-[C(=O)]_{0-1}-N(R^a)_2$,
(19) $-C(=O)-N(R^a)-C_{1-4}$ alkyl substituted with 1 or 2 $-OR^a$,
(20) $-SO_2R^a$,
(21) $-N(R^a)SO_2R^a$,

(22) -C_{2-4} alkenyl,

(23) -C_{2-4} alkenyl-C(=O)-$N(R^a)_2$,

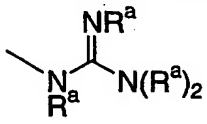
(24) -C_{2-3} alkynyl,

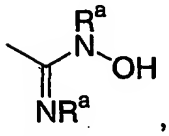
(25) $—C{\equiv}C—CH_2N(R^a)_2$,

(26) $—C{\equiv}C—CH_2OR^a$,

(27) $—C{\equiv}C—CH_2SR^a$,

(28) $—C{\equiv}C—CH_2SO_2R^a$,

(29)  ,

(30)  ,

(31) -$N(R^a)$-C_{1-4} alkyl-SR^a,

(32) -$N(R^a)$-C_{1-4} alkyl-OR^a,

(33) -$N(R^a)$-C_{1-4} alkyl-$N(R^a)_2$,

(34) -$N(R^a)$-C_{1-4} alkyl-$N(R^a)$-$C(R^a)$=O,

(35) -$N(R^a)$-C_{0-4} alkyl-$[C(=O)]_{1-2}N(R^a)_2$,

(36) -$N(R^a)$-C_{1-4} alkyl-CO_2R^a,

(37) -$N(R^a)C(=O)N(R^a)$-C_{1-4} alkyl-$C(=O)N(R^a)_2$,

(38) -$N(R^a)C(=O)$-C_{1-4} alkyl-$N(R^a)_2$,

(39) -$N(R^a)$-SO_2-$N(R^a)_2$,

(40) -R^k,

(41) -C_{1-4} alkyl substituted with R^k,

(42) -C_{1-4} fluoroalkyl substituted with R^k,

(43) -C_{2-5} alkenyl-R^k,

(44) -C_{2-5} alkynyl-R^k,

(45) -O-R^k,

(46) -O-C_{1-4} alkyl-R^k,

(47) -$S(O)_n$-R^k,

(48) -$S(O)_n$-C_{1-4} alkyl-R^k,

(49) -O-C_{1-4} alkyl-OR^k,

(50) -O-C_{1-4} alkyl-O-C_{1-4} alkyl-R^k,

(51) -O-C_{1-4} alkyl-$S(O)_nR^k$,

(52) $-N(R^c)-R^k$,
(53) $-N(R^c)-C_{1-4}$ alkyl substituted with one or two R^k groups,
(54) $-N(R^c)-C_{1-4}$ alkyl-OR^k,
(55) $-C(=O)-R^k$,
(56) $-C(=O)N(R^a)-R^k$,
(57) $-N(R^a)C(=O)-R^k$,
(58) $-C(=O)N(R^a)-C_{1-4}$ alkyl-R^k, or
(59) $-N(R^a)-C_{0-4}$ alkyl-$S(O)_nR^k$;

Q^3 is
(1) -H,
(2) $-C_{1-4}$ alkyl,
(3) $-C_{1-4}$ fluoroalkyl,
(4) $-O-C_{1-4}$ alkyl,
(5) $-O-C_{1-4}$ fluoroalkyl,
(6) halo selected from -F, -Cl, and -Br,
(7) -CN,
(8) $-C_{1-4}$ alkyl-OR^a, or
(9) $-C_{1-4}$ alkyl substituted with R^k; or

(ii) alternatively, Q^2 and Q^3 together with the carbon atoms to which they are attached and the fused ring carbon atom attached therebetween form a 5- or 6-membered monocyclic heterocycle, wherein the heterocycle contains 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur, and wherein the heterocycle is optionally substituted with from 1 to 3 substituents independently selected from
(1) $-C_{1-4}$ alkyl,
(3) $-C_{1-4}$ fluoroalkyl,
(4) $-O-C_{1-4}$ alkyl,
(5) $-O-C_{1-4}$ fluoroalkyl,
(6) halo,
(7) -CN,
(8) $-C_{1-4}$ alkyl-OR^a,
(9) $-C_{1-4}$ alkyl-$S(O)_nR^a$,
(10) $-C_{1-4}$ alkyl-$N(R^a)_2$,

(11) -C_{1-4} alkyl-C(=O)-$N(R^a)_2$,
(12) -C_{1-4} alkyl-CO_2R^a,
(13) oxo,
(14) -R^k, and
(15) -C_{1-4} alkyl substituted with R^k;

Q^4 is:

(1) -H,
(2) -C_{1-4} alkyl,
(3) -C_{1-4} fluoroalkyl,
(4) -O-C_{1-4} alkyl,
(5) -O-C_{1-4} fluoroalkyl,
(6) halo selected from -F, -Cl, and -Br,
(7) -CN,
(8) -C_{1-6} alkyl-OR^a,
(9) -$N(R^a)_2$, or
(10) -C_{1-6} alkyl -$N(R^a)_2$;

each of R^1 and R^2 is independently:

(1) -H,
(2) -C_{1-4} alkyl,
(3) -C_{1-4} fluoroalkyl,
(4) -O-C_{1-4} alkyl,
(5) -O-C_{1-4} fluoroalkyl,
(6) -OH,
(7) halo,
(8) -CN,
(9) -C_{1-4} alkyl-OR^a,
(10) -$(CH_2)_{0-2}C(=O)R^a$,
(11) -$(CH_2)_{0-2}CO_2R^a$,
(12) -$(CH_2)_{0-2}SR^a$,
(13) -$N(R^a)_2$,
(14) -C_{1-4} alkyl $N(R^a)_2$,
(15) -$(CH_2)_{0-2}C(=O)N(R^a)_2$,

(16) -C_{1-4} alkyl-$N(R^a)$-$C(R^a)$=O,
(17) -SO_2R^a,
(18) -$N(R^a)SO_2R^a$,
(19) -O-C_{1-4} alkyl-OR^a,
(20) -O-C_{1-4} alkyl-SR^a,
(21) -O-C_{1-4} alkyl-NH-CO_2R^a,
(22) -O-C_{2-4} alkyl-$N(R^a)_2$,
(23) -$N(R^a)$-C_{1-4} alkyl-SR^a,
(24) -$N(R^a)$-C_{1-4} alkyl-OR^a,
(25) -$N(R^a)$-C_{1-4} alkyl-$N(R^a)_2$,
(26) -$N(R^a)$-C_{1-4} alkyl-$N(R^a)$-$C(R^a)$=O,
(27) -R^k,
(28) -C_{1-4} alkyl substituted with 1 or 2 R^k groups,
(29) -C_{1-4} fluoroalkyl substituted with 1 or 2 R^k groups,
(30) -O-R^k,
(31) -O-C_{1-4} alkyl-R^k,
(32) -$S(O)_n$-R^k,
(33) -$S(O)_n$-C_{1-4} alkyl-R^k,
(34) -O-C_{1-4} alkyl-OR^k,
(35) -O-C_{1-4} alkyl-O-C_{1-4} alkyl-R^k,
(36) -O-C_{1-4} alkyl-$S(O)_nR^k$, or
(37) -C_{0-4} alkyl-$N(R^b)(R^k)$;

each of R^3 and R^4 is independently
(1) -H,
(2) halo,
(3) -CN,
(4) -OH,
(5) C_{1-4} alkyl,
(6) C_{1-4} fluoroalkyl,
(7) -O-C_{1-4} alkyl,
(8) -O-C_{1-4} fluoroalkyl,
(9) -C_{1-4} alkyl-OR^a,
(10) -O-C_{1-4} alkyl-OR^a,

(11) -O-C_{1-4} alkyl-SR^a,
(12) -O-C_{1-4} alkyl-NH-CO_2R^a, or
(13) -O-C_{2-4} alkyl-$N(R^a)_2$;

R^5 is

(1) -H,
(2) -C_{1-4} alkyl, optionally substituted with 1 or 2 substituents independently selected from halogen, -O-C_{1-4} alkyl, -O-C_{1-4} fluoroalkyl, $-N(R^a)_2$, and $-CO_2R^a$;
(3) phenyl optionally substituted with from 1 to 3 substituents independently selected from halogen, C_{1-4} alkyl, C_{1-4} fluoroalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} fluoroalkyl, -S-C_{1-4} alkyl, -CN, and -OH, or
(4) -C_{1-4} alkyl substituted with phenyl;

each R^a is independently -H or -C_{1-4} alkyl;

each R^b is independently:

(1) -H,
(2) -C_{1-4} alkyl,
(3) -C_{1-4} fluoroalkyl,
(4) $-R^k$,
(5) -C_{1-4} alkyl-R^k,
(6) $-S(O)_n-R^k$, or
(7) $-C(=O)-R^k$;

each R^c is independently

(1) -H,
(2) -C_{1-4} alkyl,
(3) -C_{1-4} alkyl substituted with $-N(R^a)_2$, or
(4) -C_{1-4} alkyl-phenyl, wherein the phenyl is optionally substituted with 1 to 3 substituents independently selected from halogen, C_{1-4} alkyl, C_{1-4} fluoroalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} fluoroalkyl, -S-C_{1-4} alkyl, -CN, and -OH;

each R^k is independently:

(1) aryl selected from phenyl and naphthyl, wherein aryl is unsubstituted or substituted with from 1 to 5 substituents independently selected from:

(a) halogen,
(b) C_{1-6} alkyl,
(c) C_{1-6} fluoroalkyl,
(d) -O-C_{1-6} alkyl,
(e) -O-C_{1-6} fluoroalkyl,
(f) phenyl,
(g) -S-C_{1-6} alkyl,
(h) -CN,
(i) -OH,
(j) phenyloxy, unsubstituted or substituted with from 1 to 3 substituents independently selected from:
  (i) halogen,
  (ii) C_{1-6} alkyl,
  (iii) C_{1-6} fluoroalkyl, and
  (iv) -OH,
(k) $-N(R^a)_2$,
(l) -C_{1-6} alkyl-$N(R^a)_2$,
(m) $-R^t$,
(p) $-(CH_2)_{0-3}C(=O)N(R^a)_2$, and
(q) $-(CH_2)_{0-3}C(=O)R^a$;

(2) -C_{3-7} cycloalkyl, unsubstituted or substituted with from 1 to 3 substituents independently selected from:

(a) halogen,
(b) C_{1-6} alkyl,
(c) -O-C_{1-6} alkyl,
(d) C_{1-6} fluoroalkyl,
(e) -O-C_{1-6} fluoroalkyl,
(f) -CN,
(h) phenyl, and
(j) -OH;

(3) -C_{3-7} cycloalkyl fused with a phenyl ring, unsubstituted or substituted with from 1 to 5 substituents independently selected from:

(a) halogen,
(b) C_{1-6} alkyl,
(c) -O-C_{1-6} alkyl,
(d) C_{1-6} fluoroalkyl,
(e) -O-C_{1-6} fluoroalkyl,
(f) -CN, and
(g) -OH;

(4) a 5- or 6- membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur, wherein the heteroaromatic ring is unsubstituted or substituted on nitrogen or carbon with from 1 to 5 substituents independently selected from:

(a) halogen,
(b) C_{1-6} alkyl,
(c) C_{1-6} fluoroalkyl,
(d) -O-C_{1-6} alkyl,
(e) -O-C_{1-6} fluoroalkyl,
(f) phenyl,
(g) -S-C_{1-6} alkyl,
(h) -CN,
(i) -OH,
(j) phenyloxy, unsubstituted or substituted with from 1 to 3 substituents independently selected from:
  (i) halogen,
  (ii) C_{1-6} alkyl,
  (iii) C_{1-6} fluoroalkyl, and
  (iv) -OH,
(k) -$N(R^a)_2$,
(l) -C_{1-6} alkyl-$N(R^a)_2$,
(m) -R^t,
(n) oxo,
(o) -$(CH_2)_{0-3}C(=O)N(R^a)_2$, and
(p) -$(CH_2)_{0-3}C(=O)R^a$;

(5) a 5- or 6- or 7- membered saturated heterocyclic ring containing from 1 to 3 heteroatoms independently selected from oxygen, nitrogen and sulfur, wherein the heterocyclic ring is unsubstituted or substituted with from 1 to 4 substituents independently selected from:

(a) halogen,
(b) C_{1-6} alkyl,
(c) -O-C_{1-6} alkyl,
(d) C_{1-6} fluoroalkyl,
(e) -O-C_{1-6} fluoroalkyl,
(f) -CN,
(g) oxo,
(h) phenyl
(i) benzyl,
(j) phenylethyl,
(k) -OH,
(l) $-(CH_2)_{0-3}C(=O)N(R^a)_2$,
(m) $-(CH_2)_{0-3}C(=O)R^a$,
(n) $-N(R^a)-C(=O)R^a$,
(o) $-N(R^a)-CO_2R^a$,
(p) $-(CH_2)_{1-3}N(R^a)-C(=O)R^a$,
(q) $-N(R^a)_2$,
(r) $-(CH_2)_{1-3}N(R^a)_2$,
(s) $-(CH_2)_{1-3}-OR^a$,
(t) $-(CH_2)_{0-3}CO_2R^a$,
(u) $-(CH_2)_{0-3}-O-(CH_2)_{1-3}-OR^a$,
(v) $-SO_2R^a$,
(w) $-SO_2N(R^a)_2$,
(x) $-(CH_2)_{0-3}C(=O)O(CH_2)_{1-2}CH=CH_2$,
(y) $-R^t$,
(z) $-(CH_2)_{0-3}C(=O)R^t$,
(aa) $-N(R^a)R^t$, and
(bb) $-(CH_2)_{1-3}R^t$; or

(6) an 8- to 10- membered heterobicyclic ring containing from 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur, wherein the

heterobicyclic ring is saturated or unsaturated, and is unsubstituted or substituted with from 1 to 5 substituents independently selected from:

(a) halogen,
(b) C_{1-6} alkyl,
(c) -O-C_{1-6} alkyl,
(d) C_{1-6} fluoroalkyl,
(e) -O-C_{1-6} fluoroalkyl,
(f) -CN,
(g) =O, and
(h) -OH;

R^t is naphthyl or a 5- or 6-membered heteromonocylic ring containing from 1 to 4 nitrogen atoms, wherein the heteromonocyclic ring is saturated or unsaturated, and wherein the naphthyl or the heteromonocyclic ring is unsubstituted or substituted with from 1 to 4 substituents independently selected from halogen, oxo, C_{1-4} alkyl, and -O-C_{1-4} alkyl; and

n is an integer equal to 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein

Z^1 is CH;

Q^2 is

(1) -H,
(2) -C_{1-4} alkyl,
(3) -$(CH_2)_{0-2}CF_3$,
(4) -O-C_{1-4} alkyl,
(5) -O-$(CH_2)_{0-2}CF_3$,
(6) halo selected from -F, -Cl and -Br,
(7) -CN,
(8) -$(CH_2)_{1-3}OR^a$,

(9) -$(CH_2)_{0-2}C(=O)R^a$,

(10) -$(CH_2)_{0-2}CO_2R^a$,

(11) -$(CH_2)_{0-2}SR^a$,

(12) -$N(R^a)_2$,

(13) -$(CH_2)_{1-3}N(R^a)_2$,

(14) -$(CH_2)_{0-2}C(=O)N(R^a)_2$,

(15) -G-$(CH_2)_{1-2}$-$C(=O)N(R^a)_2$, wherein G is O, S, $N(R^a)$, or $N(SO_2R^a)$,

(16) -$N(R^a)$-$C(R^a)$=O,

(17) -$(CH_2)_{1-2}$-$N(R^a)$-$C(R^a)$=O,

(18) -C(=O)-$N(R^a)$-$(CH_2)_{1-3}$-$[C(=O)]_{0-1}$-$N(R^a)_2$,

(19) -C(=O)-$N(R^a)$-$(CH_2)_{1-2}$H substituted with 1 or 2 -OR^a,

(20) -SO_2R^a,

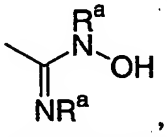
(21) -$N(R^a)SO_2R^a$,

(22) -CH=CH-$(CH_2)_{0-1}$-C(=O)-$N(R^a)_2$,

(23) —C≡C—CH_2OR^a,

(24) —C≡C—CH_2SR^a,

(25) —C≡C—$CH_2SO_2R^a$,

(26)  ,

(27) -$N(R^a)$-$(CH_2)_{1-4}SR^a$,

(28) -$N(R^a)$-$(CH_2)_{1-4}OR^a$,

(29) -$N(R^a)$-$(CH_2)_{1-4}$-$N(R^a)_2$,

(30) -$N(R^a)$-$(CH_2)_{1-4}N(R^a)$-$C(R^a)$=O,

(31) -$N(R^a)$-$(CH_2)_{0-2}$-$[C(=O)]_{1-2}N(R^a)_2$,

(32) -$N(R^a)$-$(CH_2)_{1-4}$-CO_2R^a,

(33) -$N(R^a)C(=O)N(R^a)$-$(CH_2)_{1-4}$-$C(=O)N(R^a)_2$,

(34) -$N(R^a)C(=O)$-$(CH_2)_{1-4}$-$N(R^a)_2$,

(35) -$N(R^a)$-SO_2-$N(R^a)_2$,

(36) -R^k,

(37) -$(CH_2)_{1-4}R^k$,

(38) —C≡C—CH_2R^k,

(39) -O-R^k,

(40) -$S(O)_n$-R^k,

(41) -N(R^c)-R^k,
(42) -N(R^c)-$(CH_2)_{1-4}$H substituted with one or two R^k groups,
(43) -N(R^c)-$(CH_2)_{1-4}OR^k$,
(44) -C(=O)-R^k,
(45) -C(=O)N(R^a)-R^k,
(46) -N(R^a)C(=O)-R^k, or
(47) -C(=O)N(R^a)-$(CH_2)_{1-4}R^k$; and
(48) -N(R^a)-$S(O)_nR^k$;

Q^4 is -H;

each of R^1 and R^2 is independently:
(1) -H,
(2) -C_{1-4} alkyl,
(3) -$(CH_2)_{0-2}CF_3$,
(4) -O-C_{1-4} alkyl,
(5) -O-$(CH_2)_{0-2}CF_3$,
(6) -OH,
(7) halo selected from -F, -Cl and -Br,
(8) -CN,
(9) -$(CH_2)_{1-3}OR^a$,
(10) -$(CH_2)_{0-2}C(=O)R^a$,
(11) -$(CH_2)_{0-2}CO_2R^a$,
(12) -$(CH_2)_{0-2}SR^a$,
(13) -$N(R^a)_2$,
(14) -$(CH_2)_{1-3}N(R^a)_2$,
(15) -$(CH_2)_{0-2}C(=O)N(R^a)_2$,
(16) -C_{1-4} alkyl-N(R^a)-C(R^a)=O,
(17) -SO_2R^a,
(18) -N(R^a)SO_2R^a,
(19) -O-$(CH_2)_{1-4}OR^a$,
(20) -O-$(CH_2)_{1-4}SR^a$,
(21) -O-$(CH_2)_{1-4}$NH-CO_2R^a,
(22) -O-$(CH_2)_{2-4}N(R^a)_2$,

(23) $-N(R^a)-(CH_2)_{1-4}SR^a$,
(24) $-N(R^a)-(CH_2)_{1-4}OR^a$,
(25) $-N(R^a)-(CH_2)_{1-4}N(R^a)_2$,
(26) $-N(R^a)-(CH_2)_{1-4}N(R^a)-C(R^a)=O$,
(27) $-R^k$,
(28) $-(CH_2)_{1-4}H$ substituted with 1 or 2 R^k groups,
(29) $-O-R^k$,
(30) $-O-(CH_2)_{1-4}R^k$,
(31) $-S(O)_n-R^k$,
(32) $-S(O)_n-(CH_2)_{1-4}R^k$,
(33) $-O-(CH_2)_{1-4}OR^k$,
(34) $-O-(CH_2)_{1-4}-O-(CH_2)_{1-4}R^k$,
(35) $-O-(CH_2)_{1-4}SR^k$, or
(36) $-(CH_2)_{0-4}N(R^b)(R^k)$;

each of R^3 and R^4 is independently

(1) -H,
(2) halo selected from -F, -Cl and -Br,
(3) -CN,
(4) -OH,
(5) C_{1-4} alkyl,
(6) $-(CH_2)_{0-2}CF_3$,
(7) $-O-C_{1-4}$ alkyl, or
(8) $-O(CH_2)_{0-2}CF_3$; and

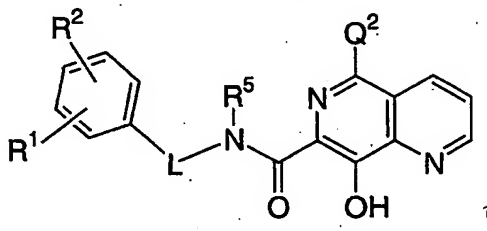
R^5 is

(1) -H,
(2) $-C_{1-4}$ alkyl,
(3) $-(CH_2)_{1-4}N(R^a)_2$,
(4) $-(CH_2)_{1-4}CO_2R^a$,
(5) phenyl optionally substituted with from 1 to 3 substituents independently selected from halogen, C_{1-4} alkyl, $-(CH_2)_{0-2}CF_3$, $-O-C_{1-4}$ alkyl, $-O(CH_2)_{0-2}CF_3$, $-S-C_{1-4}$ alkyl, -CN, and -OH, or

(6) -$(CH_2)_{1-4}$-phenyl;

or a pharmaceutically acceptable salt thereof.

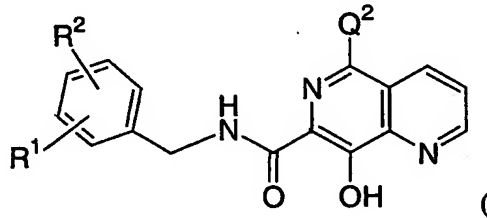
3. The compound according to claim 2, which is a compound of Formula (II):



(II);

or a pharmaceutically acceptable salt thereof.

4. The compound according to claim 3, which is a compound of Formula (III):



(III);

or a pharmaceutically acceptable salt thereof.

5. A compound according to claim 1, which is a compound selected from the group consisting of

N-1-(7-{[(4-fluorobenzyl)amino]carbonyl}-8-hydroxy-1,6-naphthyridin-5-yl)-N-1-,N-2-,N-2-trimethylethanediamide ;

5-(1,1-dioxido-1,2-thiazinan-2-yl)-*N*-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide;

N-(4-fluorobenzyl)-5-(1,1-dioxido-1,2,5-thiadiazepan-2-yl)-8-hydroxy-[1,6]napthyridine-7-carboxamide;

N-[4-fluoro-2-(methylsulfonyl)benzyl]-8-hydroxy-5-(1,1-dioxido-1,2-thiazinan-2-yl)-1,6-naphthyridine-7-carboxamide

and pharmaceutically acceptable salts thereof.

6. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

7. A method of inhibiting HIV integrase, for preventing or treating infection by HIV, or for preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

SEQUENCE LISTING

<110> Nevilel J. Anthony
Robert P. Gomez
Steven D. Young
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<120> Aza- and Polyaza-Naphthalenyl
Carboxamides Useful As HIV Integrase Inhibitors

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<213> Artificial Sequence

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<223> Synthetic DNA

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/030931 A3

(54) Title: AZA- AND POLYAZA-NAPHTHALENYL CARBOXAMIDES USEFUL AS HIV INTEGRASE INHIBITORS

(57) Abstract: Aza- and polyaza-naphthalenyl carboxamide derivatives including certain quinoline carboxamide and naphthyridine carboxamide derivatives are described. These compounds are inhibitors of HIV integrase and inhibitors of HIV replication, and are useful in the prevention or treatment of infection by HIV and the treatment of AIDS, as compounds or pharmaceutically acceptable salts, or as ingredients in pharmaceutical compositions, optionally in combination with other antivirals, immunomodulators, antibiotics or vaccines. Methods of preventing, treating or delaying the onset of AIDS and methods of preventing or treating infection by HIV are also described.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/42564

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 A61K31/4375 A61K31/4985 A61P31/12
//(C07D471/04,221:00,221:00),(C07D471/04,241:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 11073 A (PHARMACIA & UPJOHN) 19 March 1998 (1998-03-19) claims 1,8	1,6
A	WO 96 25399 A (US GOVERNMENT ;GEORGIA TECH RES INST (US)) 22 August 1996 (1996-08-22) claims 1-5,15,16	1,6,7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 June 2002	01/07/2002

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Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/42564

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 7 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/42564

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9811073 A	19-03-1998	AU 4172197 A	02-04-1998
		EP 0927164 A1	07-07-1999
		JP 2002505660 T	19-02-2002
		WO 9811073 A1	19-03-1998
		US 6252080 B1	26-06-2001
		US 6211376 B1	03-04-2001
		US 6310211 B1	30-10-2001
WO 9625399 A	22-08-1996	US 5681832 A	28-10-1997
		AU 4985596 A	04-09-1996
		WO 9625399 A1	22-08-1996